Diagnosis and management of obesity hypoventilation syndrome in the ICU

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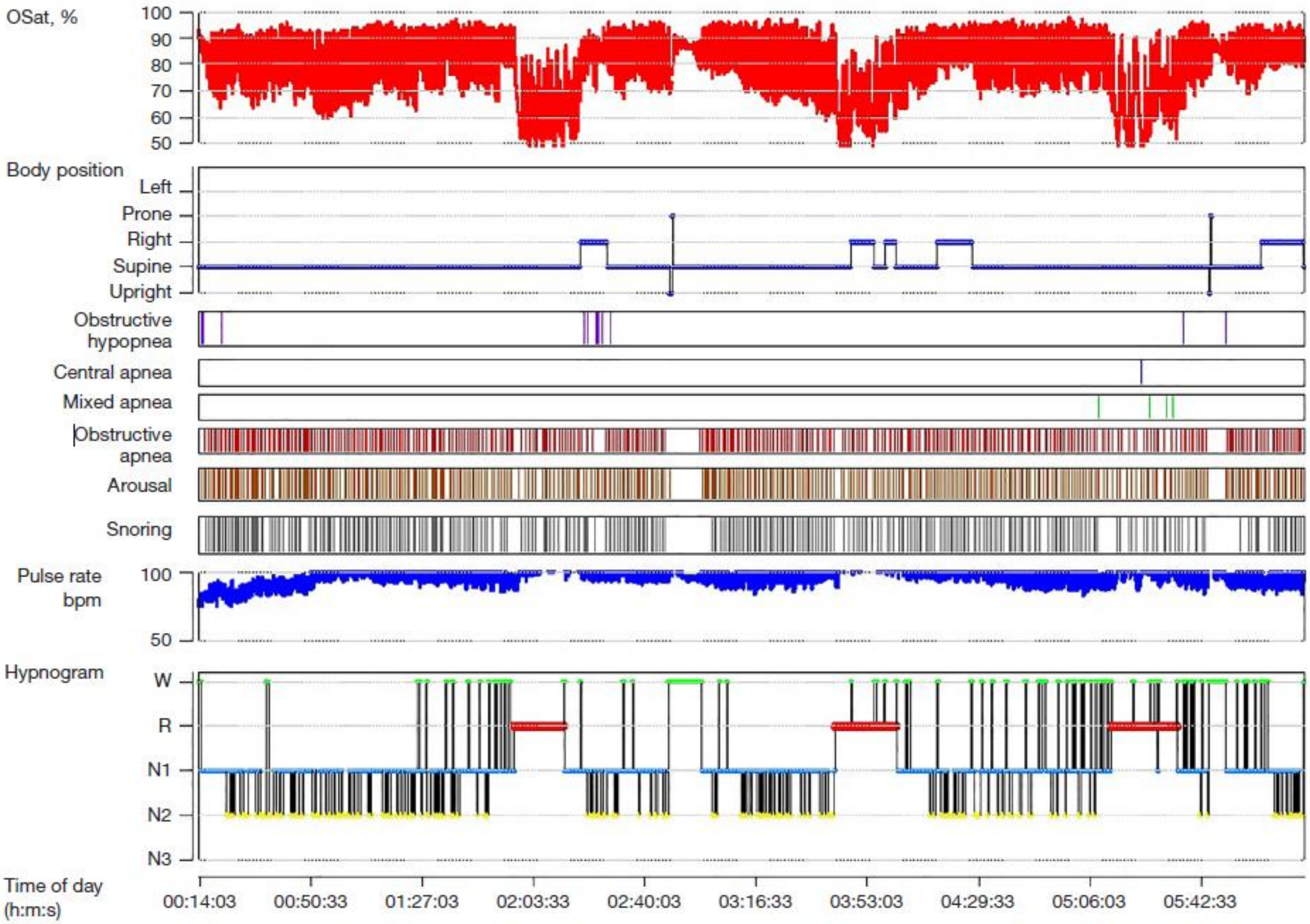
CASE: M/58

- Admitted to the cardiac ICU d/t dyspnea
- Previous healthy except CHB (w/o LC), never smoked
- Weight 129 kg, height 175cm, BMI 42 kg/m^2
- V/S 151/98-98-22-37.1℃
- ABGA on ambient air: 7.38-72-44-42, 75%
- NT-proBNP 1,150 pg/mL
- EchoCG: LVEF 70%, D-shaped LV; RV, dilated, systolic function ↓; PASP 67mmHg
- Chest CT: no PE
- HFNC 60 L/min, FiO_2 0.8

  (without an NIV mask of helmet?)
- Progressed respiratory failure → MV → VV-ECMO on day 1
- Diuretics, negative net fluid balance, and nutritional controls
- VV-ECMO weaned on day 19
- Extubation and nocturnal NIV on day 26
- Weight 98 kg, BMI 32 kg/m^2 on week 4

→ Diagnosis of obesity hypoventilation syndrome

Ann Palliat Med 2022;11:3341-5.



OSat, %
100
90
80
70
60
50
Body position
Left
Prone
Right
Supine
Upright
Obstructive hypopnea
Central apnea
Mixed apnea
Obstructive apnea
Arousal
Snoring
Pulse rate bpm
100
50
Hypnogram
W
R
N1
N2
N3
Time of day (h:m:s)
00:14:03
00:50:33
01:27:03
02:03:33
02:40:03
03:16:33
03:53:03
04:29:33
05:06:03
05:42:33

CLINICAL AND PHYSIOLOGICAL ASPECTS OF A CASE OF OBESITY, POLYCYTHEMIA AND ALVEOLAR HYPOVENTILATION

By J. HOWLAND AUCHINCLOSS, Jr., ELLEN COOK, and ATTILIO D. RENZETTI

(From the Department of Medicine, State University of New York, Upstate Medical Center at Syracuse, N. Y.)

(Submitted for publication March 31, 1955; accepted June 22, 1955)

The occurrence of arterial hypoxia with polycythemia usually results from some known type of pulmonary disease or from an abnormal communication between the right and left sides of the circulation. Although arterial oxygen unsaturation has been observed in patients with polycythemia vera (1–4), it is usually of only mild degree. Recently, Newman, Feltman, and Devlin (5) found polycythemia and a severe degree of arterial hypoxia in two patients who did not have evidence of any previously described form of lung disease. These authors postulated that polycythemia vera by its effects on the lung or on the respiratory center could give rise to oxygen unsaturation of arterial blood. They also suggested that in some patients polycythemia is secondary to respiratory center disease of undetermined etiology.

The significant laboratory findings were as follows: red blood cells 6.77 million per cu. mm.; hemoglobin 20 gm. per cent; hematocrit 69 per cent; white blood cells 6,000 per cu. mm. with a normal differential count and normal cellular morphology; platelets 150,000 per cu. mm. The bone marrow showed hyperplasia of the erythroid series, and reticulocytes were 1 per cent of the red blood cells. The blood uric acid was 9.6 mg. per cent. The urinary 17-ketosteroid excretion was 8 mg. in twenty-four hours (normal). X-ray of the chest showed cardiac enlargement and enlargement of the pulmonary vessels. Angiocardiography showed filling of the cardiac chambers in normal sequence. The sella turcica appeared normal by X-ray. An electrocardiogram showed evidence of right ventricular hypertrophy.

Treatment consisted of bed rest, digitalis, sodium and caloric restriction, mercurials and, beginning on the sixth day, repeated phlebotomies. By the end of seventeen days after his date of entry into the hospital a total of five liters of blood had been removed. The patient lost twenty-four pounds in the first five days and an additional thirty pounds before leaving the hospital. He be-

CLINICAL REPORT

C. D., a thirty-year old white man was admitted to the hospital on January 8, 1954 complaining of shortness of breath and ankle swelling. He had weighed more than 200 pounds for at least 13 years. In 1942 he worked as a furnace feeder in an aluminum plant for six months. He first noted a non-productive cough in 1950 and since then had experienced an increased frequency of respiratory infections. In March, 1952, an elevated hematocrit was observed, and by October, 1952 he had to stop work because of dyspnea and ankle edema. In the six months before entering the hospital these symptoms increased, and he developed orthopnea.

Physical examination revealed an alert, cyanotic, slightly orthopneic man who weighed 290 pounds and was 67 inches in height. A few rales were heard at the right posterior lung base. The heart was in gallop rhythm, and the pulmonic second sound was accentuated. Mild edema of the abdominal wall and marked edema of the lower extremities was present.

AUCHINCLOSS JH Jr, et al. J Clin Invest. 1955 Oct;34(10):1537-45.

Case Reports

Extreme Obesity Associated with Alveolar Hypoventilation—A Pickwickian Syndrome*

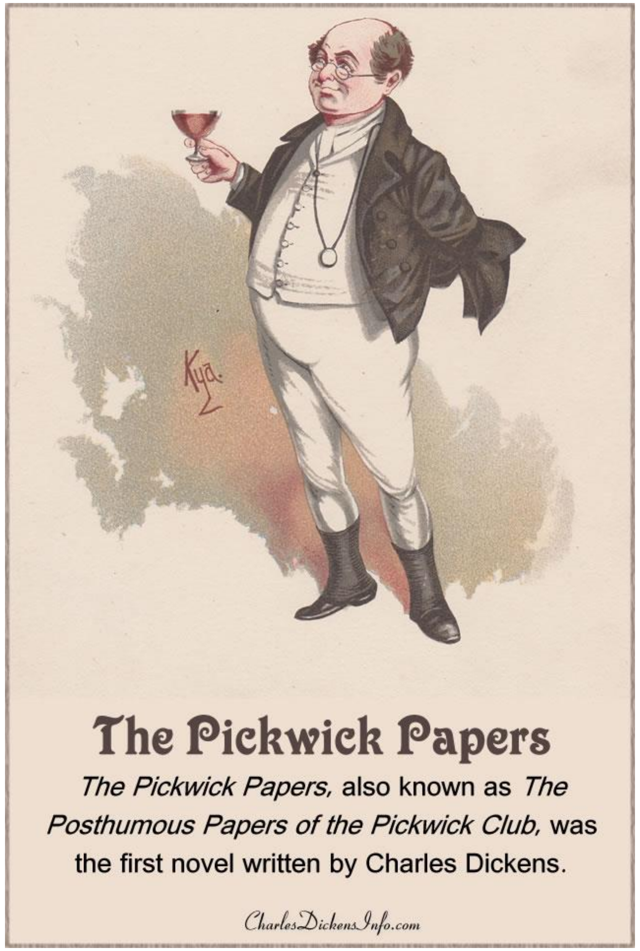
C. Sidney Burwell, M.D., Eugene D. Robin, M.D., Robert D. Whaley, M.D. *and* Albert G. Bickelmann, M.D.†

Boston, Massachusetts

The purpose of this article is to consider the association of obesity, somnolence, polycythemia and excessive appetite. A careful study of one patient will be used to illustrate the discussion.

he is sitting up or even while he is engaged in conversation or other muscular activity. The somnolence of his character was described by Mr. Dickens in the following words:

"A most violent and startling knocking was



BICKELMANN AG, et al. Am J Med. 1956 Nov;21(5):811-8.

Obesity hypoventilation syndrome (OHS)

- Obesity: BMI ≥ 30 kg/m^2
- Daytime hypercapnia: $PaCO_2$ ≥ 45 mmHg during wakefulness
- Absence of an alternative neuromuscular, mechanical, or metabolic explanation for hypoventilation.

- Sleep-disordered breathing (SDB): invariably accompanied by SDB, and therefore SDB is included as one of the diagnostic criteria in some expert definitions of OHS

Principles and Practice of Sleep Medicine (7th edition)

SBD in OHS

Obesity

- Body mass index ≥ 30 kg/m^2

Chronic Hypoventilation

- Awake daytime hypercapnia (sea-level arterial Pco_2 ≥ 45 mm Hg)

Sleep-Disordered Breathing

- Obstructive sleep apnea (apnea-hypopnea index [AHI] ≥ 5 events/hour)
- Nonobstructive sleep hypoventilation is defined by AHI <5 events/hour and $PaCO_2$ (or a surrogate such as end-tidal PCO_2 or transcutaneous PCO_2) above 55 mm Hg for more than 10 minutes or an increase in the $PaCO_2$ (or surrogate) above 10 mm Hg compared to an awake supine value to a value exceeding 50 mm Hg for more than 10 minutes

Exclusion of Other Causes of Hypoventilation

- Severe obstructive airways disease (e.g., COPD)
- Severe interstitial lung disease
- Severe chest-wall disorders (e.g., kyphoscoliosis)
- Severe hypothyroidism
- Neuromuscular disease
- Congenital hypoventilation syndromes

- OSA (apnea-hypopnea index [AHI] ≥ 5/h: 90%
- Severe OSA (AHI ≥ 30/h): 70%
- Remaining patients have non-obstructive sleep hypoventilation with no or mild OSA.

Principles and Practice of Sleep Medicine (7th edition)
Eur Respir Rev 2019;28.

Staging of hypoventilation in obesity

TABLE 4 Staging of hypoventilation in obesity

0	At risk	BMI >30 kg·m^{-2}	OSA	No hypercapnia
I	Obesity-associated sleep hypoventilation	BMI >30 kg·m^{-2}	OSA/hypoventilation during sleep	Intermittent hypercapnia during sleep, full recovery during sleep (P_{aCO_2} or P_{tcCO_2} morning~evening) Serum bicarbonate <27 mmol·L^{-1} during wake
II	Obesity-associated sleep hypoventilation	BMI >30 kg·m^{-2}	OSA/hypoventilation during sleep	Intermittent hypercapnia during sleep (P_{aCO_2} or P_{tcCO_2} morning>evening) Serum bicarbonate ⩾27 mmol·L^{-1} during wake Bicarbonate increased during day
III	Obesity hypoventilation	BMI >30 kg·m^{-2}	OSA/hypoventilation during sleep	Sustained hypercapnia (P_{CO_2} >45 mmHg) while awake
IV	Obesity hypoventilation syndrome	BMI >30 kg·m^{-2}	OSA/hypoventilation during sleep	Sustained hypercapnia while awake, cardiometabolic comorbidities

Eur Respir J 2017;49.

Prevalence

- In the general population: unknown (estimates: 0.3% to 0.48%)
- In patients presenting with SBD

Study	Region	Year	Males, %	Age, y	BMI, kg/m^2	Pa_{CO_2}, mm Hg	Prevalence, %
Mokhlesi et al[35]	United States	2007	66	49	47	54	20
Kawata et al[36]	Japan	2007	93	49	31	47	14
Trakada et al[37]	Greece	2010	NR	57	40	57	14
Alzaabi et al[38]	United Arab Emirates	2013	61	55	45	57	17
Macavei et al[34]	United Kingdom	2013	NR	55	42	51	22
Harada et al[31]	Japan	2014	55	50	37	49	12
BaHammam[39]	Saudi Arabia	2015	33	57	45	57	8.5

- In ICU setting: unknown (one study: 8%)

Chest 2016;149:856-68.
J Intensive Care Med 2013;28:124-30.

Clinical presentations

- The most common presentations are either
  - An acute-on-chronic exacerbation of hypercapnic respiratory failure, leading to admission to an ICU or a sleep specialist referral for suspected OSA

- Patients with OHS admitted with acute hypercapnic respiratory failure have a high rate in-hospital mortality (18%).

Eur Respir J 2017;49.
J Intensive Care Med 2017;32:421-8.

Characteristics of OHS admitted to ICU (1)

- Retrospective review of all patients who were admitted to ICU over an 8-month period, September 2010 and April 2011, USA

- OHS prevalence: 8% of all admissions

	All (n = 61)
Age (years)	59 ± 11
BMI, kg/m^2	48.9 ± 8.6
$PaCO_2$, mm Hg	69.2 ± 17.4
HCO^{3-},meq/L	34.3 ± 5.1
Serum creatinine, mg/dL	1.7 ± 1.6
HbA1C, %	7.5 ± 1.8
TSH, mcu/mL	1.8 ± 1.0
Total cholesterol, mg/dL	174 ± 48
Triglyceride, mg/dL	135 ± 64
HDL, mg/dL	41 ± 17
25-OH vitamin D, ng/mL	13.5 ± 8.5
AST IU/L	36 ± 36
CRP, mg/dL	9.4 ± 6.9
NASH (%)	39 (64)
LV mass, $g/m^{2.7}$	60.9 ± 21.8
PA, systolic, mm Hg	47 ± 18

J Intensive Care Med 2013;28:124-30.

Characteristics of OHS admitted to ICU (1)

- All of the patients had been previously admitted to our hospital or emergency room in the preceding 24 months; the average number of admissions was 6+7 (range 1-39).

- 42 (68%) patients had been erroneously diagnosed and treated for COPD, 4 for asthma/COPD.
  - None of the patients diagnosed with COPD had evidence of obstructive airway disease and none of the patients diagnosed with asthma had evidence of reversible airway obstruction on lung function testing.
  - All patients were admitted to hospital with the diagnosis of "COPD exacerbation" and/or heart failure.

J Intensive Care Med 2013;28:124-30.

Characteristics of OHS admitted to ICU (1)

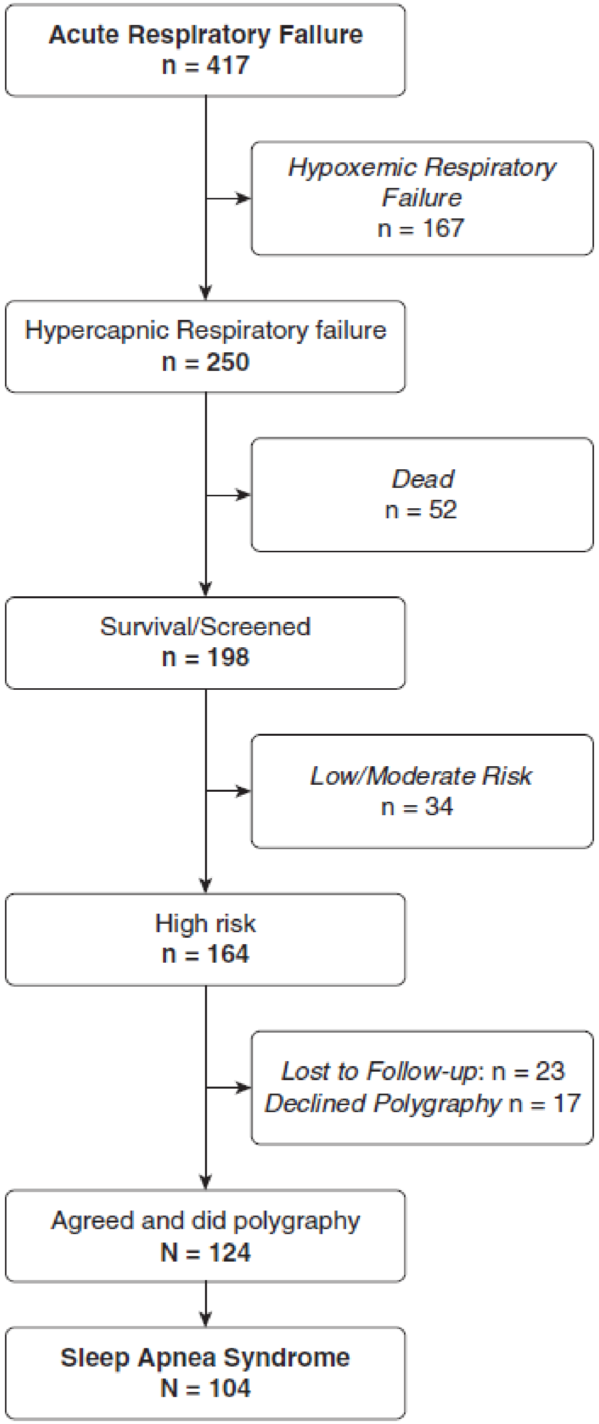
- 24 (40%) patients had previously undergone polysomnography, with 22 having been prescribed nocturnal CPAP/BiPAP; only 3 of these patients carried the diagnosis of OHS.
- 3 patients had previously had a tracheotomy performed for OSA; these patients required mechanical ventilation.

- 7 patients had a tracheotomy performed while in the ICU.
- 11 patients (18%) died during the index hospitalization
- During the 8-month period of the study, 4 patients were readmitted to the ICU while 5 remained hospitalized in our long-term ventilator facility.

J Intensive Care Med 2013;28:124-30.

Characteristics of OHS admitted to ICU (2)

- Patients consecutively admitted to the ICU for hypercapnic respiratory failure without previously diagnosed sleep apnea, between January 2015 and December 2018
- STOP-Bang questionnaire ≥ 3 → invited to type 3 sleep study within 3weeks following the ICU discharge



Ann Am Thorac Soc 2021;18:727-9.

STOP-Bang questionnaire

Yes	No	
○	○	**Snoring ?** Do you **Snore Loudly** (loud enough to be heard through closed doors or your bed-partner elbows you for snoring at night)?
○	○	**Tired ?** Do you often feel **Tired, Fatigued, or Sleepy** during the daytime (such as falling asleep during driving or talking to someone)?
○	○	**Observed ?** Has anyone **Observed** you **Stop Breathing** or **Choking/Gasping** during your sleep ?
○	○	**Pressure ?** Do you have or are being treated for **High Blood Pressure** ?
○	○	**Body Mass Index more than 35 kg/m^2?**
○	○	**Age older than 50 ?**
○	○	**Neck size large ? (Measured around Adams apple)** Is your shirt collar 16 inches / 40cm or larger?
○	○	**Gender = Male ?**

See Result

For general population

OSA - Low Risk : Yes to 0 - 2 questions

OSA - Intermediate Risk : Yes to 3 - 4 questions

OSA - High Risk : Yes to 5 - 8 questions

or Yes to 2 or more of 4 STOP questions + male gender

or Yes to 2 or more of 4 STOP questions + BMI > $35kg/m^2$

or Yes to 2 or more of 4 STOP questions + neck circumference 16 inches / 40cm

Table 2. Demographic and clinical characteristics of study patients

Variable	Value
Demographics	
Age, yr	66 ± 11
Sex, M/F	44/60
Comorbidities	
Obesity (BMI ⩾30)	83 (80)
Smoking	66 (63)
COPD	49 (48)
Obesity hypoventilation syndrome	24 (23)
Hypertension	68 (66.3)
Diabetes	37 (35.6)
Coronary artery disease	15 (14)
Cause of ICU admission	
Left ventricular failure	80 (77)
COPD tracheobronchitis	13 (12.5)
Community-acquired pneumonia	11 (10.6)
Arterial blood gas	
pH	7.29 ± 0.07
Pa_{O_2}, kPa	8.47 ± 2.5
Pa_{CO_2}, kPa	9.6 ± 3.4
CO_3H^-, mmol/L	32 ± 4
CO_3H^- ⩾27 mmol/L	78 (75)

Ann Am Thorac Soc 2021;18:727-9.

Pitfalls in the management of OHS

- Excessive oxygen administration
- Excessive administration of loop diuretics
- Misdiagnosis of obstructive lung disease

Ann Am Thorac Soc 2016;13:109-14.

Characteristics of OHS admitted to ICU

- Many obese patients have hypoxemia at baseline, which worsens with acute illness.
  - due to dependent atelectasis, hypoventilation, or other coexistent respiratory disease

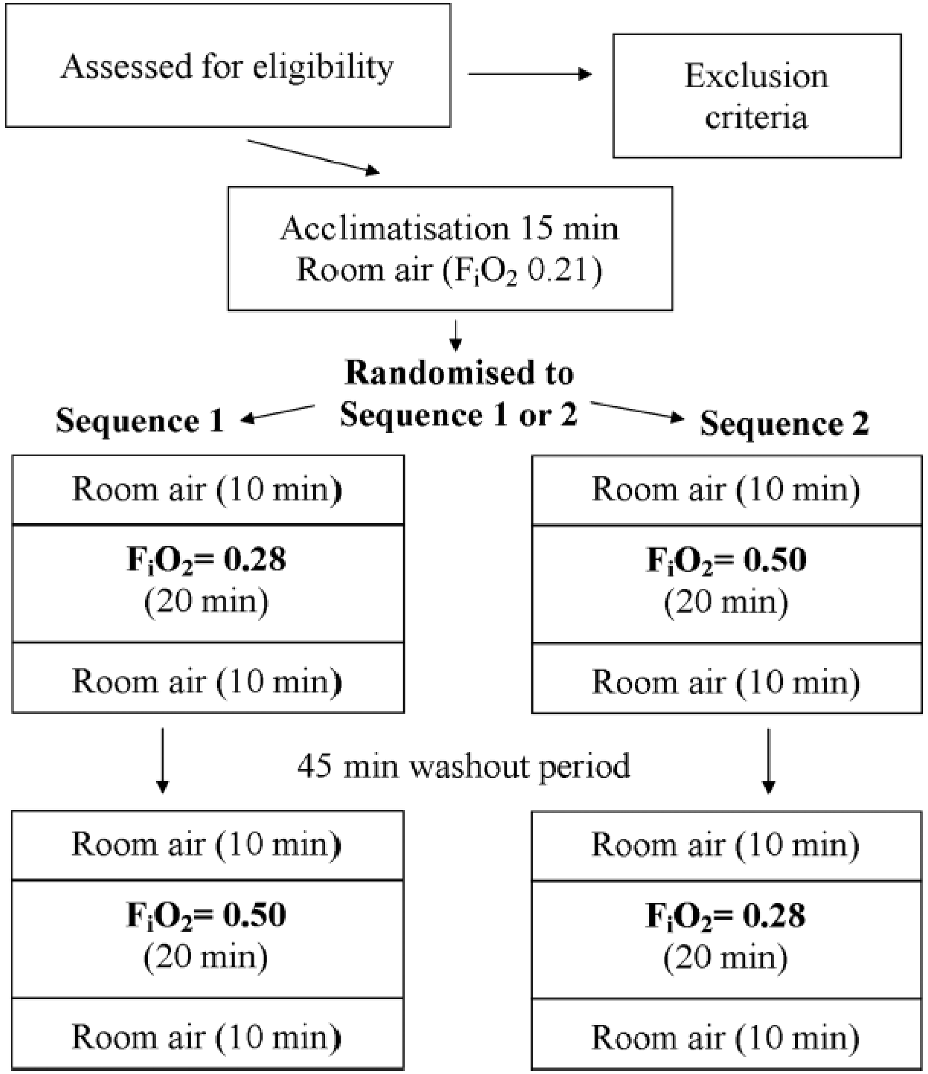
- Acute hyperoxia-induced hypercapnia: well-accepted phenomenon in COPD.

- Recommendation: titrating inspired oxygen in patients who do not require immediate intubation for airway protection or hemodynamic compromise, to yield oxygen saturations of 89 to 92%.

Ann Am Thorac Soc 2016;13:109-14.

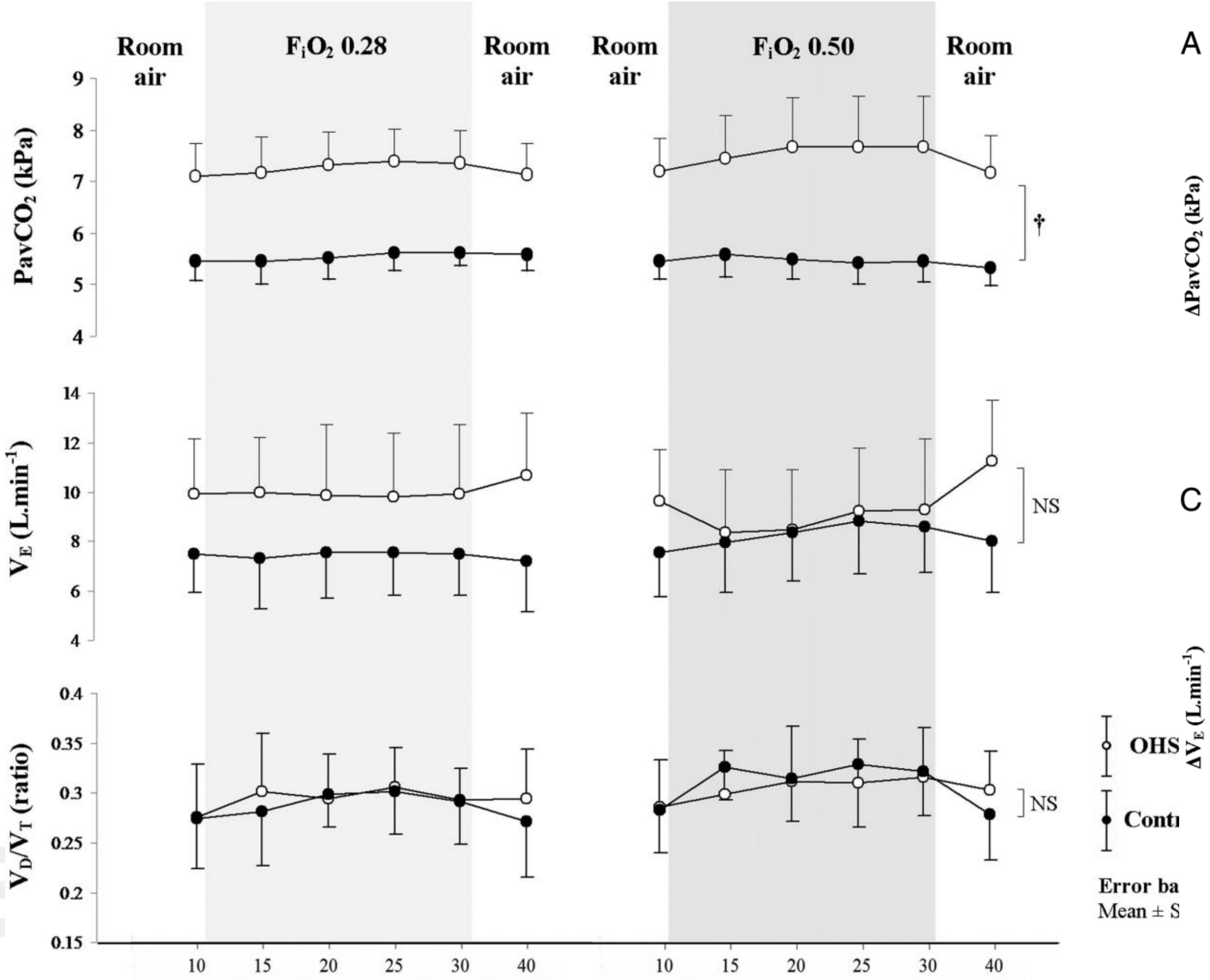
Excessive oxygen administration

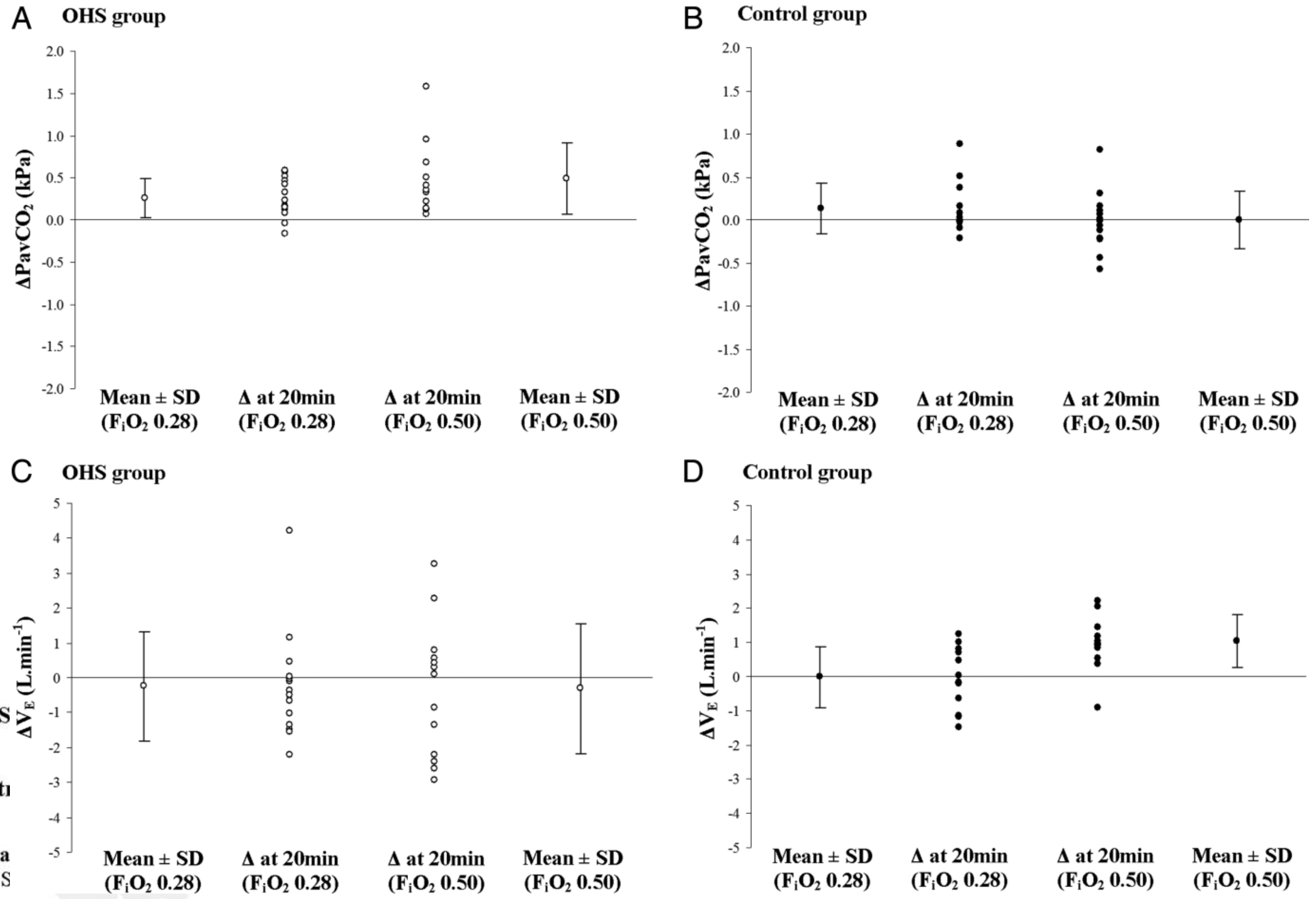
- Double-blind randomized crossover study
- 14 OHS, 14 controls



Thorax 2014;69:346-53.

Excessive oxygen administration



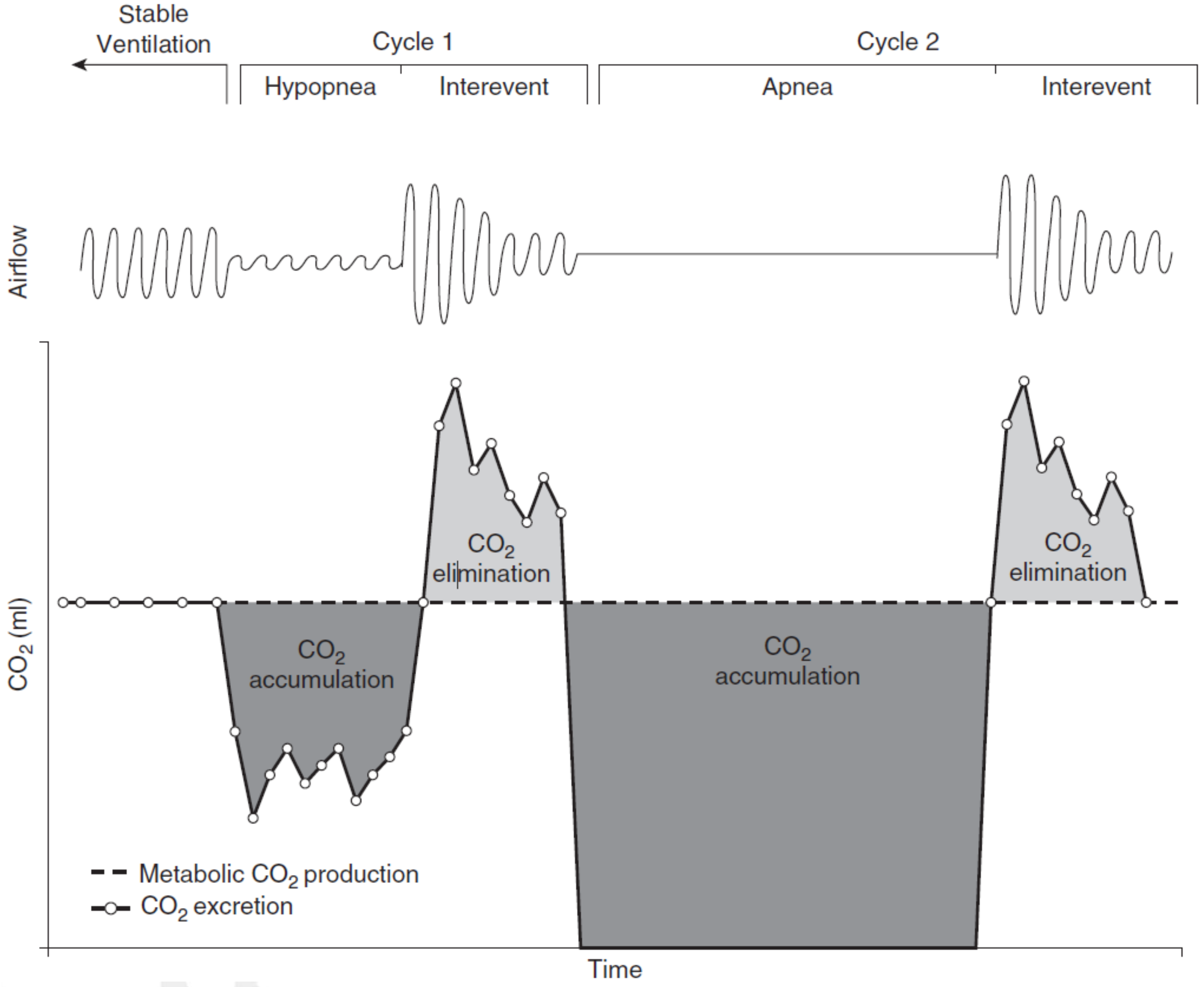


50% inspired oxygen was associated with more than 3 mm Hg increase of PCO_2 and 3% increase in dead space fraction after 20 minutes.

Thorax 2014;69:346-53.

Excessive administration of loop diuretics

- Nocturnal hypercapnia associated apnea/hypopnea causes gradual increases in bicarbonate that are not fully excreted during the day

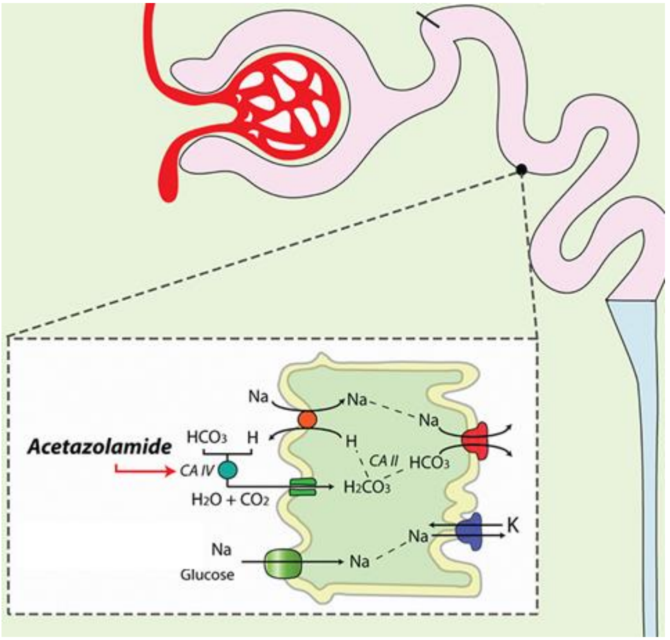


Ann Am Thorac Soc 2016;13:109-14.

Excessive administration of loop diuretics

- Lower extremity edema, pulmonary edema
- Cor pulmonale, left ventricular diastolic/systolic dysfunction

→ Frequent use of loop diuretic such as furosemide



- Overuse of furosemide → contraction alkalosis exacerbate metabolic alkalosis and associated compensatory hypercapnia.

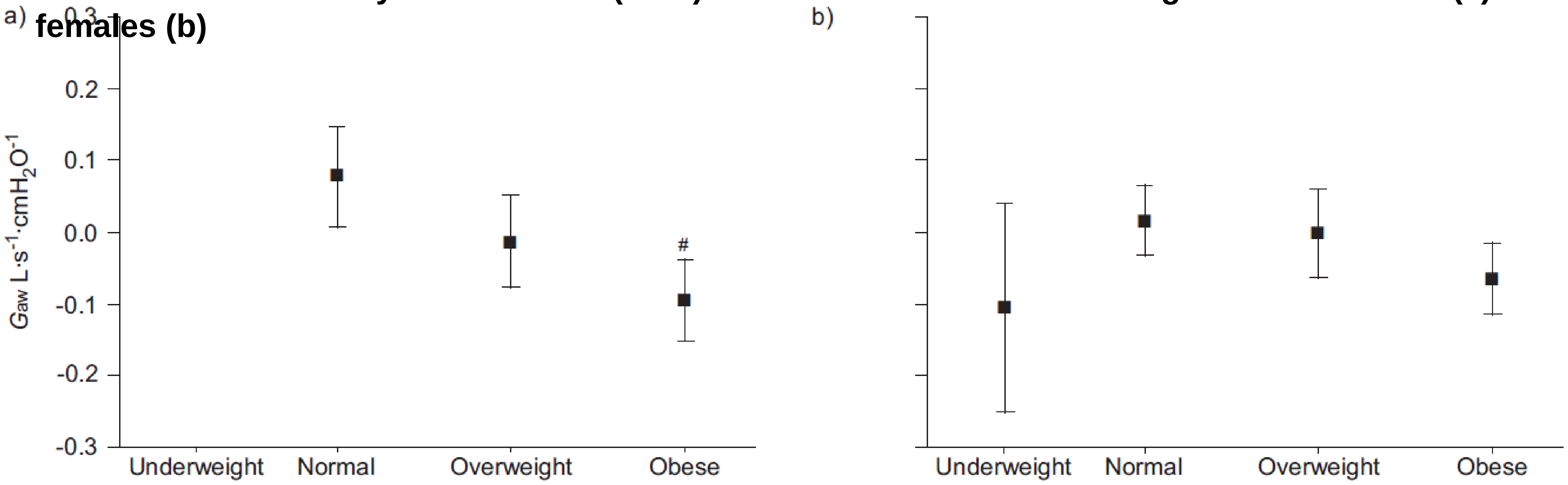
- Use of acetazolamide to offset the alkalosis promoting properties of furosemide alone.

Ann Am Thorac Soc 2016;13:109-14.

Misdiagnosis of obstructive lung disease

- There are data to suggest that obesity reduces airway caliber, which, in some patients, may cause wheezing without airway disease.

Mean±95% CI of airway conductance (Gaw) corrected for asthma and lung volume in males (a) and females (b)



Ann Am Thorac Soc 2016;13:109-14.
Eur Respir J 2005;25:896-901.

Management of acute-on-chronic exacerbations of OHS

AMERICAN THORACIC SOCIETY DOCUMENTS

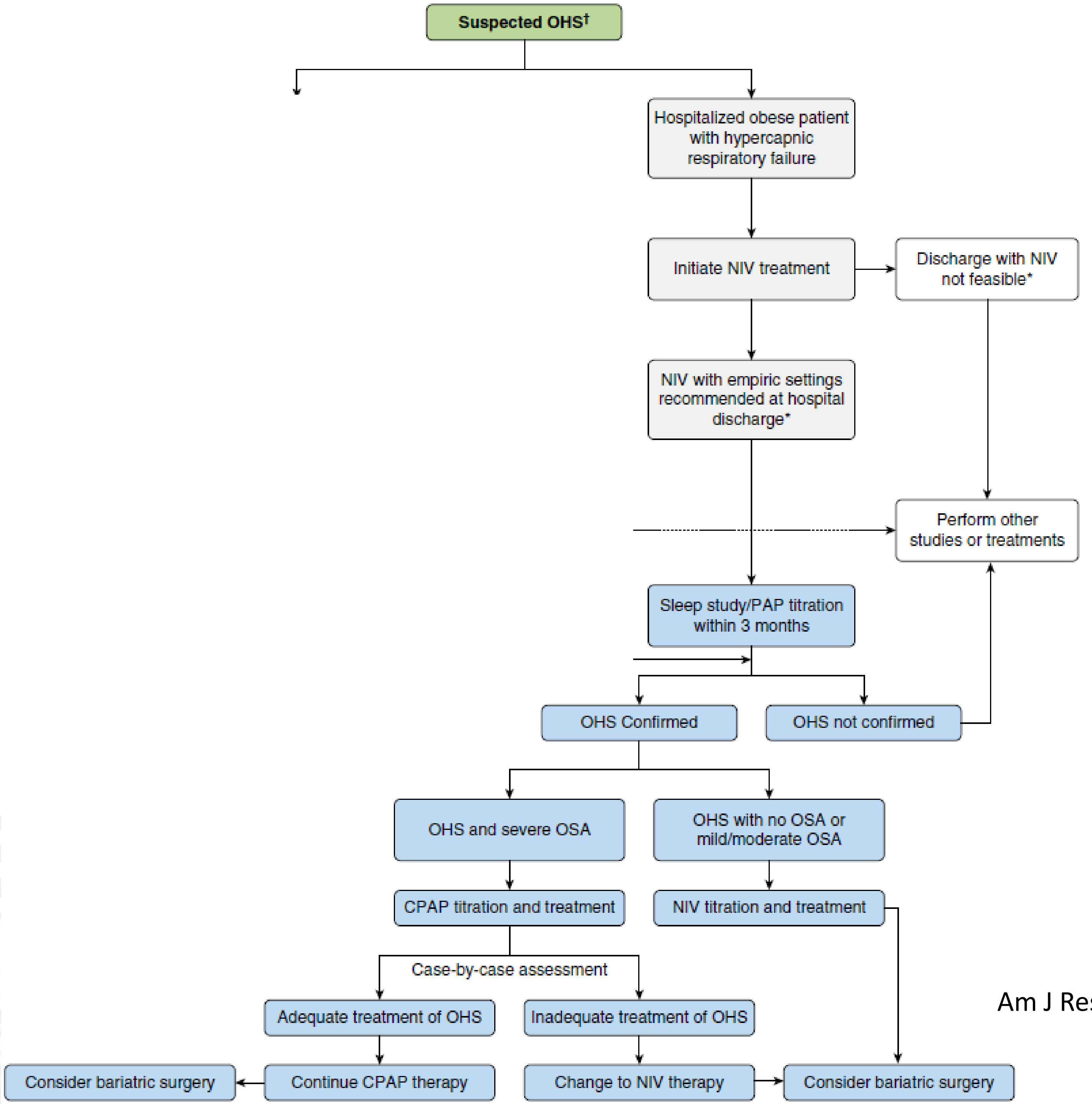
Evaluation and Management of Obesity Hypoventilation Syndrome

An Official American Thoracic Society Clinical Practice Guideline

Babak Mokhlesi, Juan Fernando Masa, Jan L. Brozek, Indira Gurubhagavatula, Patrick B. Murphy, Amanda J. Piper, Aiman Tulaimat, Majid Afshar, Jay S. Balachandran, Raed A. Dweik, Ronald R. Grunstein, Nicholas Hart, Roop Kaw, Geraldo Lorenzi-Filho, Sushmita Pamidi, Bhakti K. Patel, Susheel P. Patil, Jean Louis Pépin, Israa Soghier, Maximiliano Tamae Kakazu, and Mihaela Teodorescu; on behalf of the American Thoracic Society Assembly on Sleep and Respiratory Neurobiology

THIS OFFICIAL CLINICAL PRACTICE GUIDELINE OF THE AMERICAN THORACIC SOCIETY WAS APPROVED MAY 2019

Am J Respir Crit Care Med 2019;200:e6-e24.



Am J Respir Crit Care Med 2019;200:e6-e24.

Question 4: Should hospitalized adults suspected of having OHS, in whom the diagnosis has not yet been made, be discharged from the hospital with or without PAP treatment until the diagnosis of OHS is either confirmed or ruled out?

Individual patient data meta-analysis

- No RCT
- 9 studies, total of 1,162 patients: 1,043 (89.8%) discharged with PAP (NIV, 91.5%, CPAP 8.5%) and 119 discharged without PAP
- To mitigate confounding, patients were divided into three groups (tertiles) on the basis of propensity scores.

	PAP	No PAP	*P* Value
All patients, *N*	1,043	119	
Age, yr	65.9 ± 13.9	68.8 ± 13.7	0.03
BMI, kg/m^2	43.0 ± 7.2	42.8 ± 7.1	0.77
Baseline $PaCO_2$, mm Hg	66.9 ± 16.7	69.6 ± 17.1	0.10
Group 1	375	7	
Age, yr	65.1 ± 13.8	66.7 ± 13.8	0.76
BMI, kg/m^2	43.2 ± 7.5	43.4 ± 8.0	0.94
Baseline $PaCO_2$, mm Hg	64.9 ± 15.4	67.3 ± 17.0	0.68
Group 2	371	24	
Age, yr	65.6 ± 14.0	68.0 ± 13.7	0.42
BMI, kg/m^2	43.1 ± 7.4	43.0 ± 7.4	0.95
Baseline $PaCO_2$, mm Hg	65.5 ± 15.6	67.4 ± 16.0	0.56
Group 3	297	88	
Age, yr	66.0 ± 13.9	69.1 ± 13.6	0.07
BMI, kg/m^2	43.0 ± 7.2	42.7 ± 7.1	0.73
Baseline $PaCO_2$, mm Hg	67.0 ± 16.7	69.9 ± 17.2	0.17

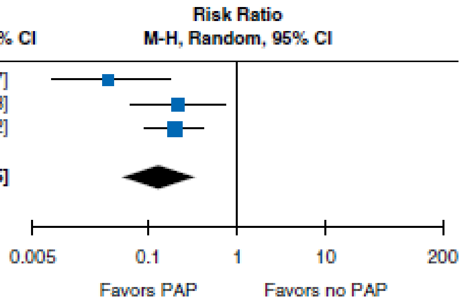
Ann Am Thorac Soc 2020;17:627-37.

3-month mortality

Study or Subgroup	PAP Events	PAP Total	No PAP Events	No PAP Total	Weight	Risk Ratio M-H, Random, 95% CI
Group 1	4	375	2	7	24.2%	0.04 [0.01, 0.17]
Group 2	10	371	3	24	31.0%	0.22 [0.06, 0.73]
Group 3	10	297	15	88	44.8%	0.20 [0.09, 0.42]
Total (95% CI)		**1043**		**119**	**100.0%**	**0.14 [0.05, 0.35]**
Total events	24		20			

Heterogeneity: $Tau^2 = 0.38$; $Chi^2 = 4.26$, df = 2 (P = 0.12); $I^2 = 53\%$

Test for overall effect: Z = 4.09 (P < 0.0001)

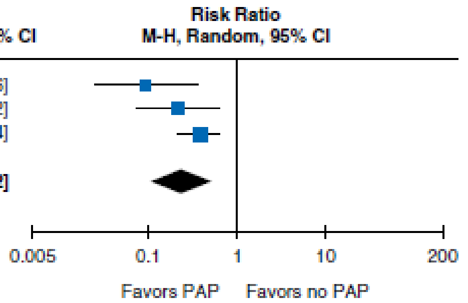


6-month mortality

Study or Subgroup	PAP Events	PAP Total	No PAP Events	No PAP Total	Weight	Risk Ratio M-H, Random, 95% CI
Group 1	10	362	2	7	22.0%	0.10 [0.03, 0.36]
Group 2	13	354	4	24	29.2%	0.22 [0.08, 0.62]
Group 3	26	285	21	88	48.8%	0.38 [0.23, 0.64]
Total (95% CI)		**1001**		**119**	**100.0%**	**0.24 [0.11, 0.52]**
Total events	49		27			

Heterogeneity: $Tau^2 = 0.24$; $Chi^2 = 4.18$, df = 2 (P = 0.12); $I^2 = 52\%$

Test for overall effect: Z = 3.63 (P = 0.0003)

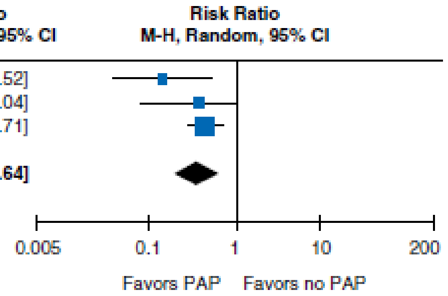


9-month mortality

Study or Subgroup	PAP Events	PAP Total	No PAP Events	No PAP Total	Weight	Risk Ratio M-H, Random, 95% CI
Group 1	15	362	2	7	16.0%	0.15 [0.04, 0.52]
Group 2	23	354	4	24	24.3%	0.39 [0.15, 1.04]
Group 3	37	285	25	88	59.7%	0.46 [0.29, 0.71]
Total (95% CI)		**1001**		**119**	**100.0%**	**0.37 [0.21, 0.64]**
Total events	75		31			

Heterogeneity: $Tau^2 = 0.08$; $Chi^2 = 2.86$, df = 2 (P = 0.24); $I^2 = 30\%$

Test for overall effect: Z = 3.54 (P = 0.0004)

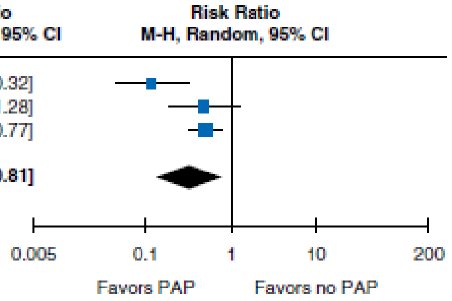


1-year mortality

Study or Subgroup	PAP Events	PAP Total	No PAP Events	No PAP Total	Weight	Risk Ratio M-H, Random, 95% CI
Group 1	19	362	3	7	29.2%	0.12 [0.05, 0.32]
Group 2	29	354	4	24	29.2%	0.49 [0.19, 1.28]
Group 3	53	285	31	88	41.6%	0.53 [0.36, 0.77]
Total (95% CI)		**1001**		**119**	**100.0%**	**0.34 [0.14, 0.81]**
Total events	101		38			

Heterogeneity: $Tau^2 = 0.44$; $Chi^2 = 8.07$, df = 2 (P = 0.02); $I^2 = 75\%$

Test for overall effect: Z = 2.44 (P = 0.01)

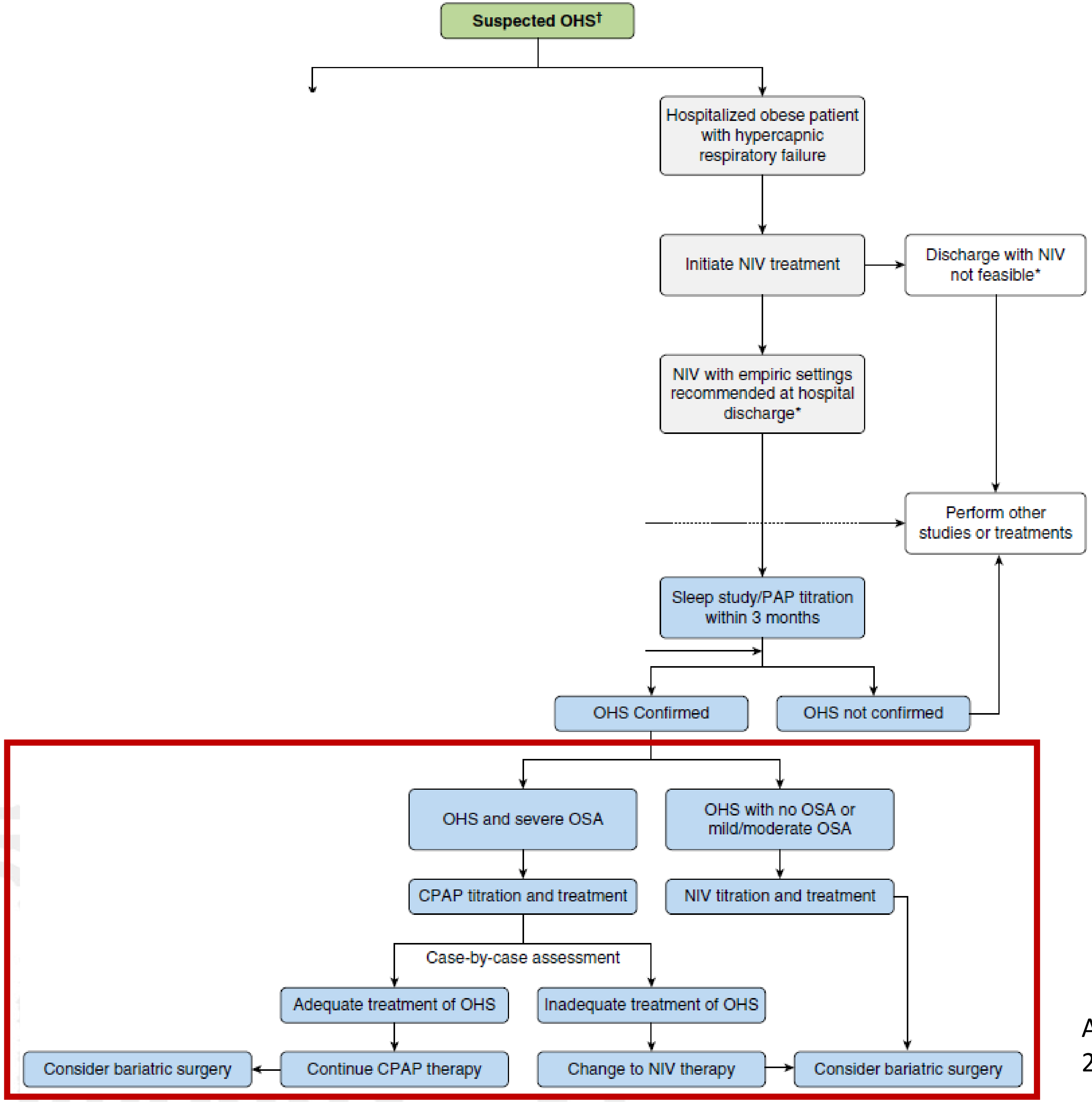


Ann Am Thorac Soc 2020;17:627-37.

Individual patient data meta-analysis

			Effects				
Number of Studies	**Study Design**	**Risk of Bias**	**Discharge with PAP**	**Discharge without PAP**	**Risk Ratio (95% CI)**	**Risk Difference**	**Number Needed to Treat (NNT)**
3-mo Mortality, All Patients							
9 (6, 18–25)	IPD-MA	serious*	24/1043 (2.3%)	20/119 (16.8%)	0.14 (0.05–0.35)	−14.5%	6.9
6-mo Mortality, All Patients							
9 (6, 18–25)	IPD-MA	serious*	49/1001 (4.9%)	27/119 (22.7%)	0.24 (0.11–0.52)	−17.8%	5.6
9-mo Mortality, All Patients							
9 (6, 18–25)	IPD-MA	serious*	75/1001 (7.5%)	31/119 (26.1%)	0.37 (0.21–0.64)	−18.6%	5.4
1-yr Mortality, All Patients							
9 (6, 18–25)	IPD-MA	serious*	101/1001 (10.1%)	38/119 (31.9%)	0.34 (0.14–0.81)	−21.8%	4.6

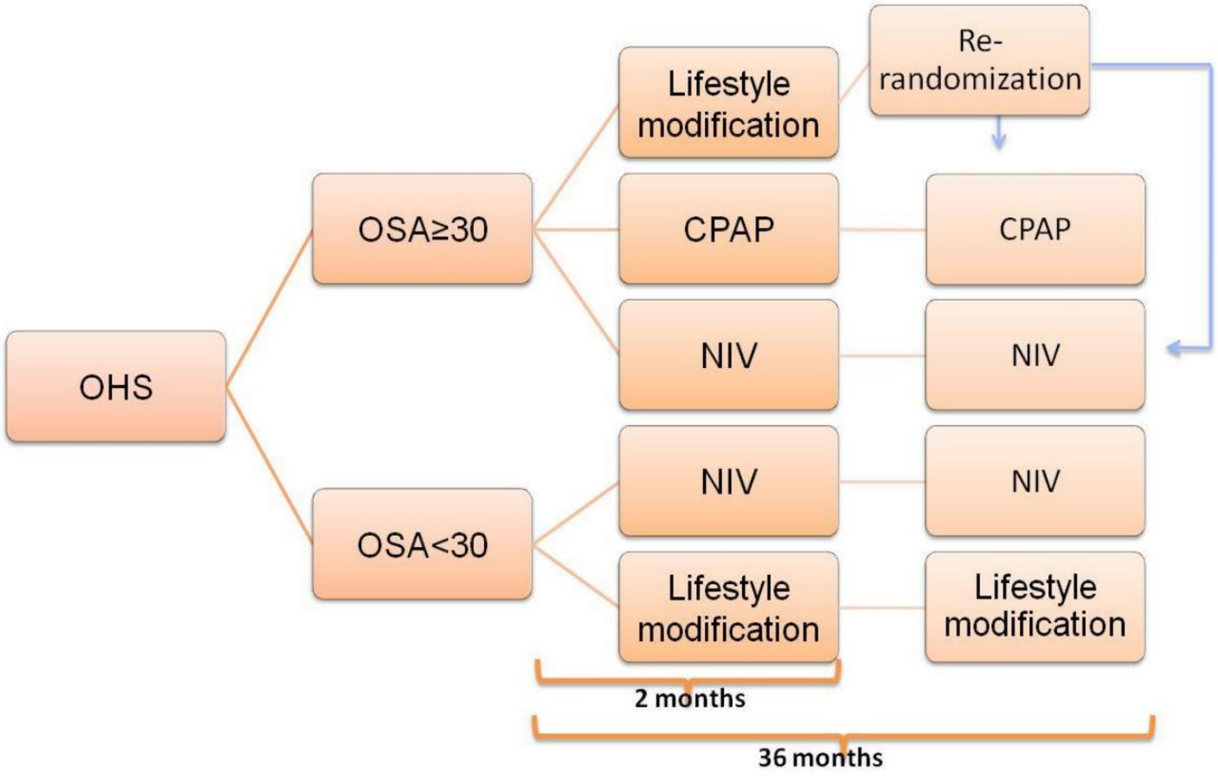
Ann Am Thorac Soc 2020;17:627-37.



Am J Respir Crit Care Med 2019;200:e6-e24.

Pickwick project

- Multicenter, open-label RCT at 16 clinical sites in Spain
- Enrolled between May 2009 and March 2013



Masa JF, et al. Am J Respir Crit Care Med. 2015 Jul 1;192(1):86-95.

Pickwick study with severe OSA

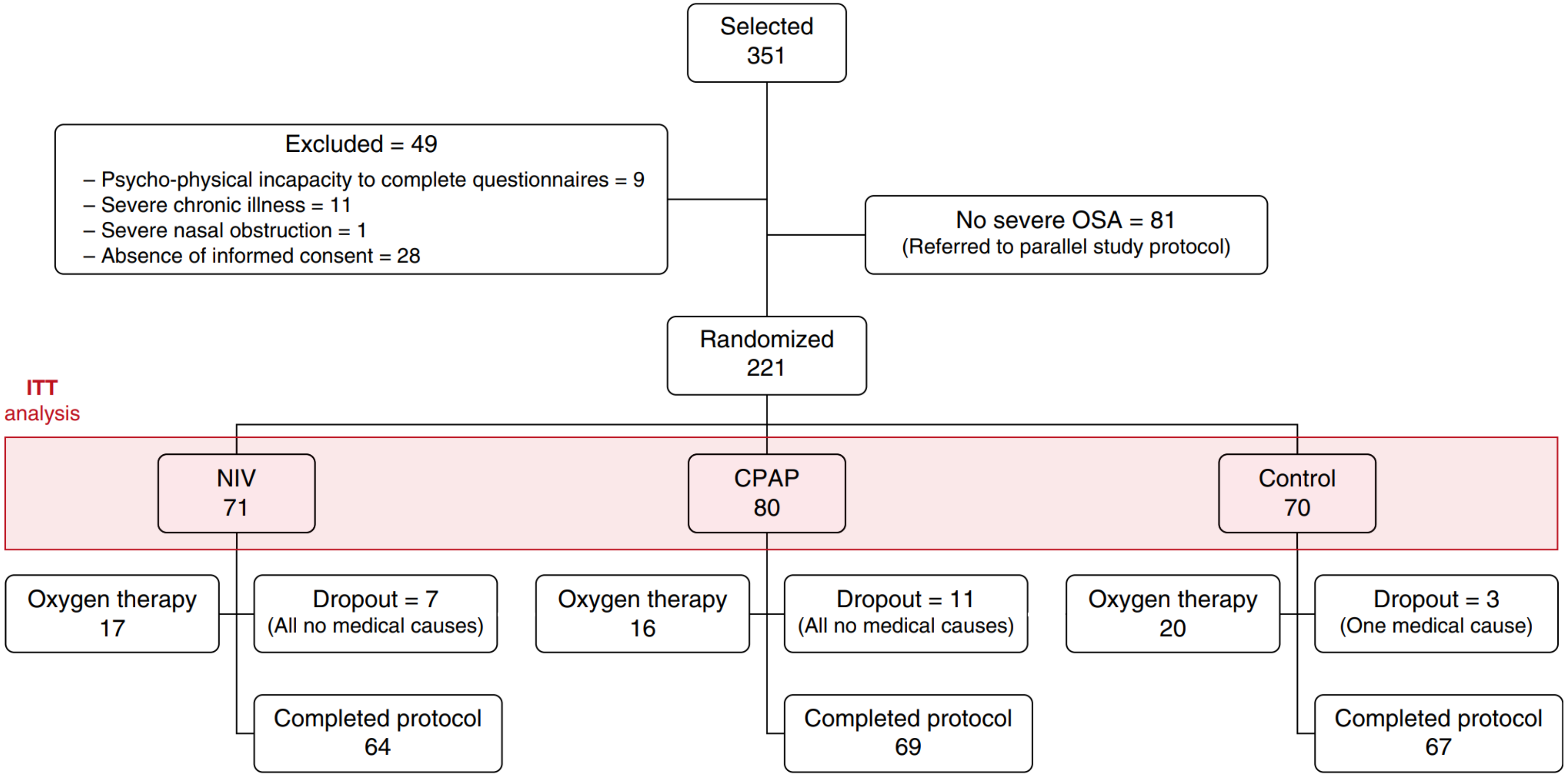
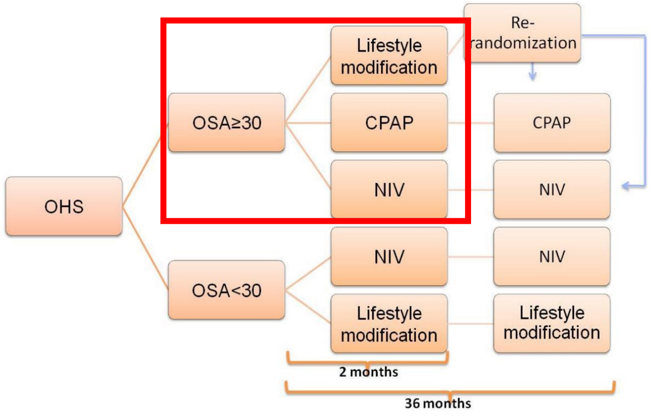


Figure 1. Flow chart of the study protocol. Of the 351 selected patients, 49 were excluded, 81 had nonsevere obstructive sleep apnea (OSA), and 221 were randomized. A dropout in the control group was due to hospital admission requiring noninvasive ventilation (NIV) treatment for more than 5 days. CPAP = continuous positive airway pressure; ITT = intention to treat.



Masa JF, et al. Am J Respir Crit Care Med. 2015 Jul 1;192(1):86-95.

30↑, 2M, Primary outcome: $PaCO_2$

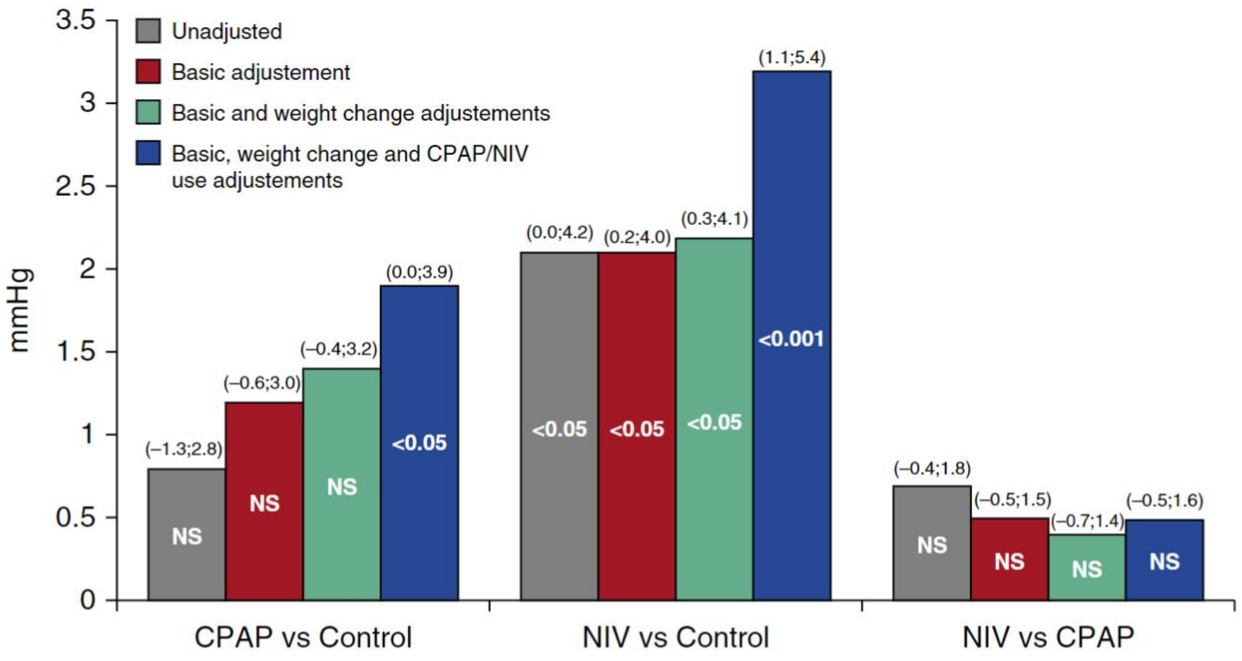


Figure 2. Intergroup Pa_{CO_2} changes (means and 95% confidential intervals), adjusted according to basic adjustments (Pa_{CO_2}, age, sex, body mass index, and apnea–hypopnea baseline values), weight change, and continuous positive airway pressure (CPAP)/noninvasive ventilation (NIV) use (more or less than 4 h/night). NS = not significant.

- NIV yielded the greatest improvement in $PaCO_2$ with significant differences.
- In the CPAP group, $PaCO_2$ improvement was significantly different than in the control.
  - only after CPAP compliance adjustment.
- No significant differences between NIV and CPAP groups.

- NIV ≒ CPAP : $PaCO_2$, bicarbonate
- NIV > CPAP : respiratory function, 6-MWD.

Masa JF, et al. Am J Respir Crit Care Med. 2015 Jul 1;192(1):86-95.

30↑, 2M, Secondary outcome

Table 2. Baseline Measurements and Changes with Treatment Related to the Primary and Secondary Outcomes of Pulmonary Function

PaCO2
Bicarbonate

Respiratory function
6-MWD

	Baseline [*Mean (SD)*]			Intragroup Differences [*Mean (SD)*]			*P* Value of Intergroup Differences	
	NIV	CPAP	Control	NIV	CPAP	Control	Unadjusted	Adjusted
Pa_{CO_2}, mm Hg	51 (4.3)	50 (4.5)	51 (4.2)	−5.5 (7)*	−3.7 (6.6)*	−3.2 (6)*	0.029	0.034
Bicarbonate, mmol/L	30 (3.4)	30 (4)	30 (3.2)	−2.1 (3.2)*	−1.9 (3.7)*	0.7 (3.1)	0.010† 0.033‡	0.005
pH	7.405 (0.032)	7.403 (0.041)	7.393 (0.036)	0.006 (0.036)	0.007 (0.032)§	0.020 (0.032)*	0.017† 0.026‡	NS
Pa_{O_2}, mm Hg	62 (8.7)	63 (9.8)	61 (8.2)	4.8 (10)*	5.5 (12)*	1.9 (8.3)	NS	
FEV_1, %	76 (17)	79 (20)	80 (20)	4.8 (13)$^{\|}$	−1.8 (15)	−1.5 (18)	0.015† 0.009¶	0.041† 0.003¶
FVC, %	78 (19)	80 (20)	82 (20)	4.1 (16)§	−1.4 (19)	−0.6 (18)	NS	—
FEV_1/FVC	80 (11)	81 (11)	80 (10)	1.5 (12)	−1.9 (9.3)	−1.7 (12)	NS	—
6-MWD, m	340 (132)	358 (131)	338 (112)	32 (58)*	6.0 (63)	16 (67)	0.013¶	0.01¶

Table 3. Baseline Values and Changes in the Epworth Sleepiness Scale Score, Health-related Quality-of-Life Test Results, and Weight

Sleepiness questionnaire

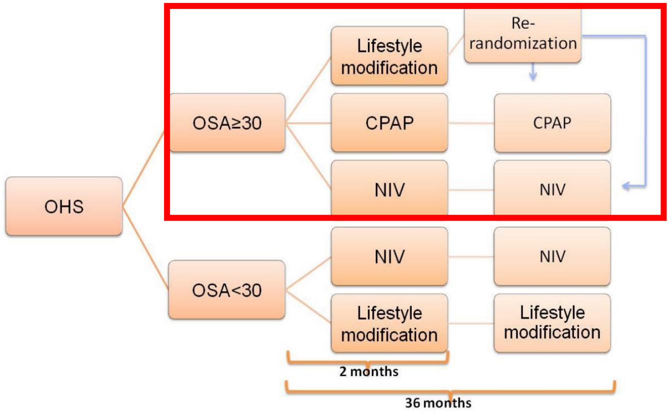
QOL questionnaire

	Baseline [*Mean (SD)*]			Intragroup Differences [*Mean (SD)*]			*P* Value of Intergroup Differences	
	NIV	CPAP	Control	NIV	CPAP	Control	Unadjusted	Adjusted
ESS	11 (5.1)	11 (4.8)	11 (5.3)	−4.8 (5)*	−4.3 (4.7)*	−1.0 (4.4)	0.000†‡	0.000†‡
FOSQ	73 (22)	71 (21)	77 (23)	4.3 (17)§	5.1 (16)$^{\|}$	−1.7 (16)	0.031† 012‡	0.027†
SF-36, physical	36 (10)	36 (10)	37 (11)	1.8 (8.7)	1.2 (8.9)	0.2 (6.8)	NS	—
SF-36, mental	44 (13)	42 (14)	44 (12)	1.7 (14)	4.6 (12)$^{\|}$	1.2 (8.8)	NS	—
VAWS	50 (22)	45 (24)	47 (19)	11 (25)*	8.1 (21)$^{\|}$	2.1 (17)	0.012†	0.003†
Weight, kg	110 (19)	117 (25)	115 (24)	−2.4 (6.6)$^{\|}$	−1.1 (5.6)	−1.6 (5.0)$^{\|}$	NS	—

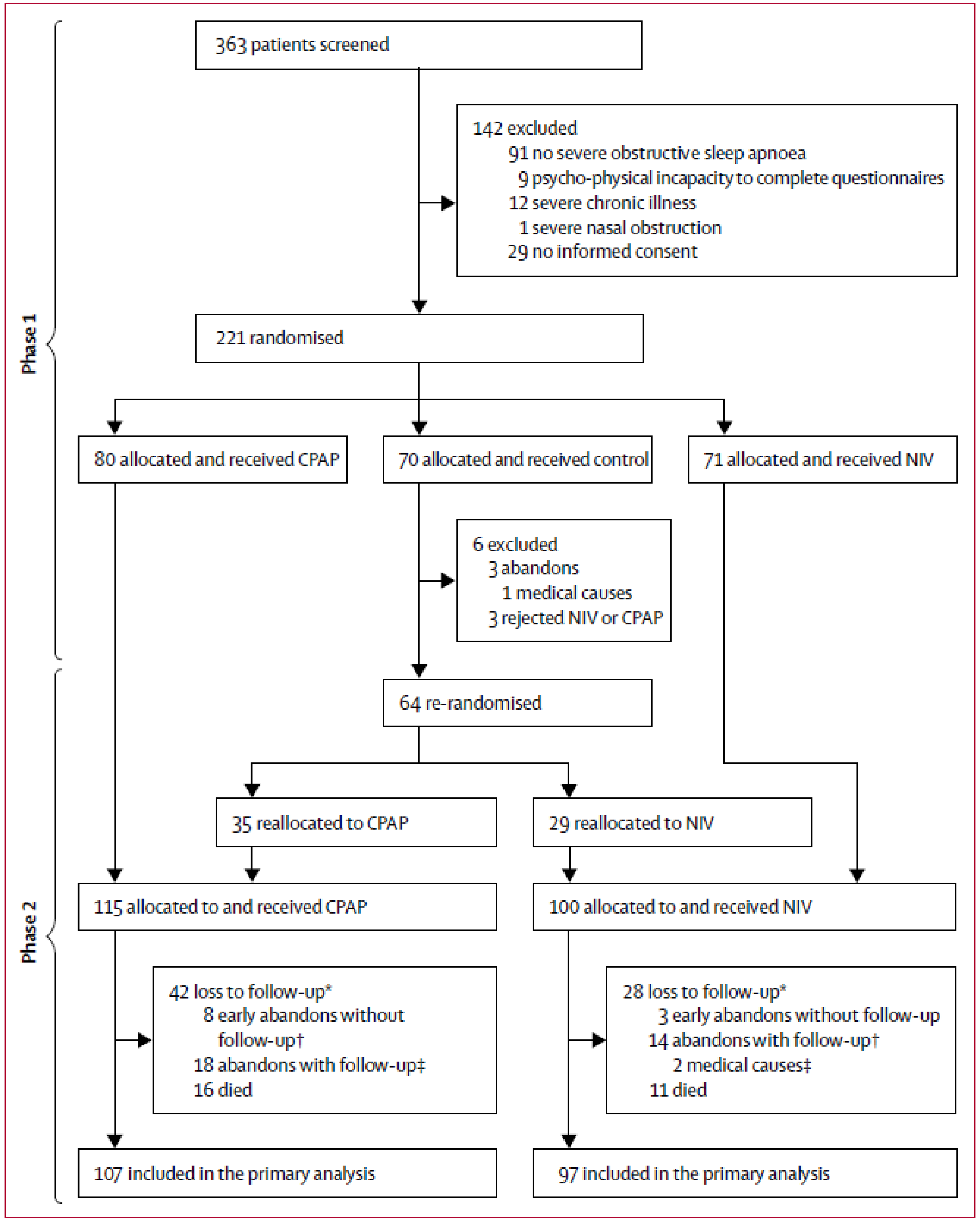
NIV ≒ CPAP : $PaCO_2$, bicarbonate
NIV > CPAP : respiratory function, 6-MWD.

Masa JF, et al. Am J Respir Crit Care Med. 2015 Jul 1;192(1):86-95.

30↑, 36 M

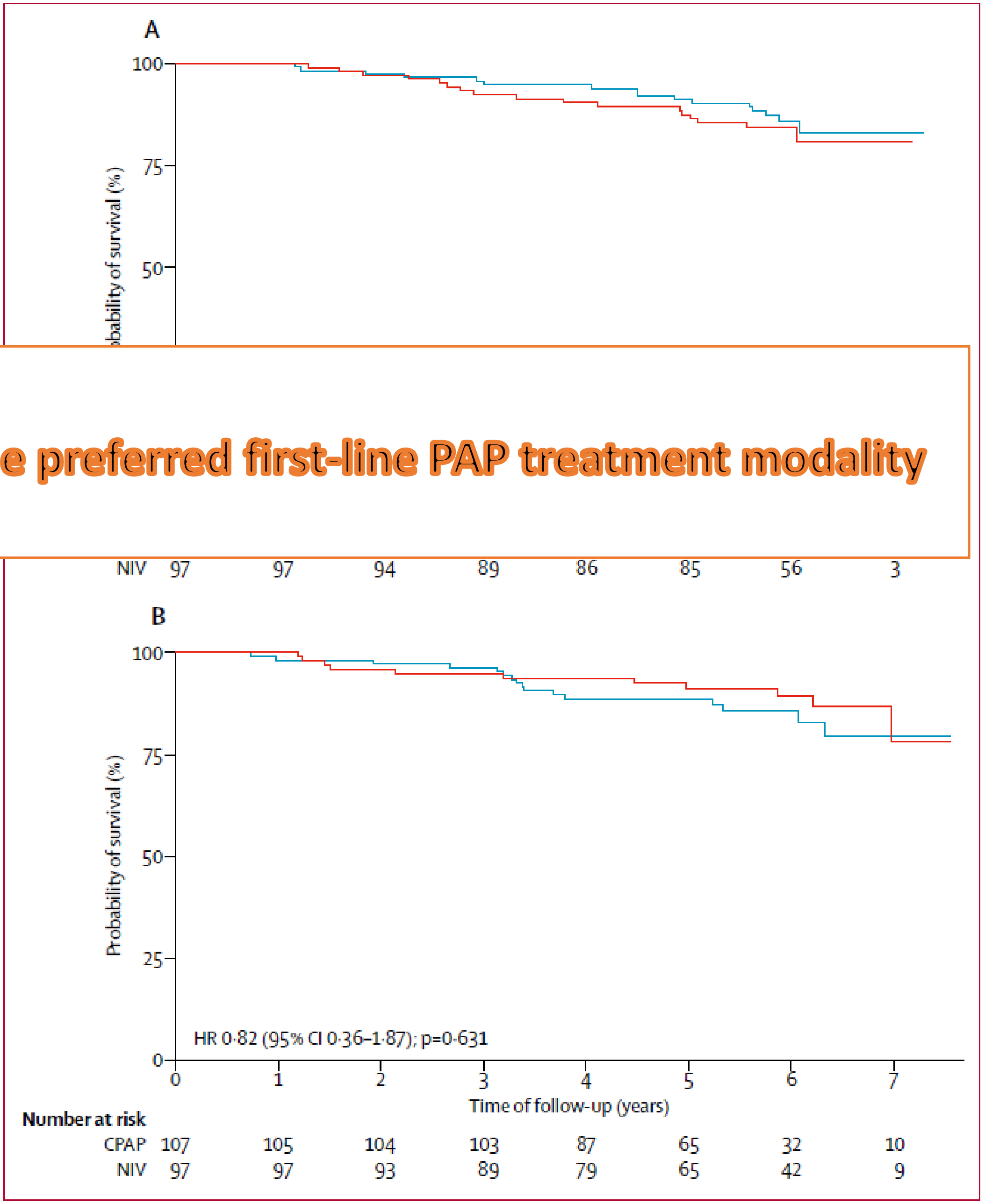


- Patients in the control group (i.e. lifestyle changes) were re-randomized.
- All patients randomized to NIV or CPAP were followed for 3 years.
- Median follow-up: 5.44 years
- **Primary outcome: hospitalization days per year**
- Median adherence to CPAP or NIV: 6.0 h/d



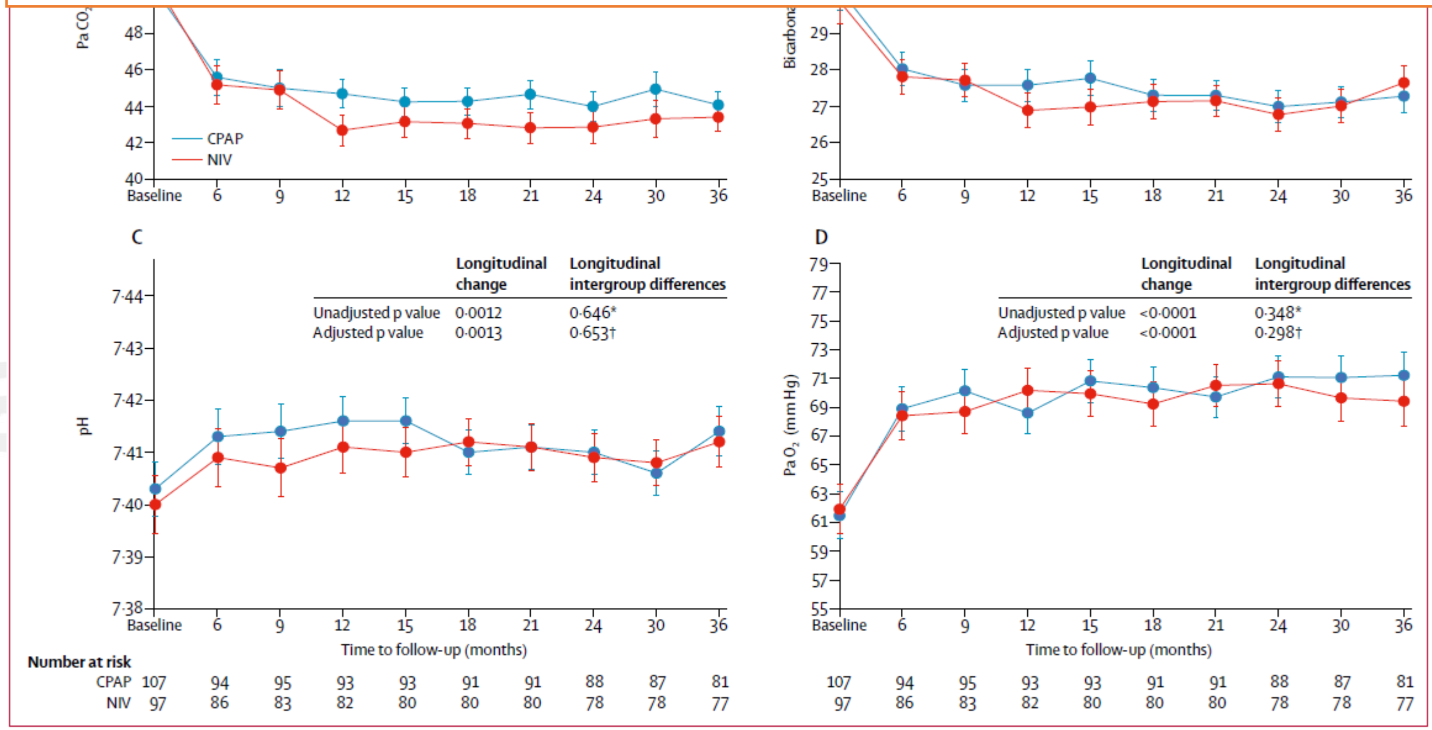
Masa JF, et al. Lancet 2019;393:1721-32.

	Continuous positive airway pressure (n=107)	Non-invasive ventilation (n=97)	Mean difference (95% CI)	Negative binomial regression	
				Adjusted rate ratio (95% CI)	p value
		Obesity hypoventilation syndrome			
Primary outcome					
Hospitalisation days (per year per patient)	1·63 (3·74)	1·44 (3·07)	−0·19 (−1·13 to 0·75)	0·78 (0·34–1·77)	0·561



Simple is the best!

Given that CPAP has lower complexity and cost, CPAP might be the preferred first-line PAP treatment modality until more studies become available.



Pickwick study without severe OSA

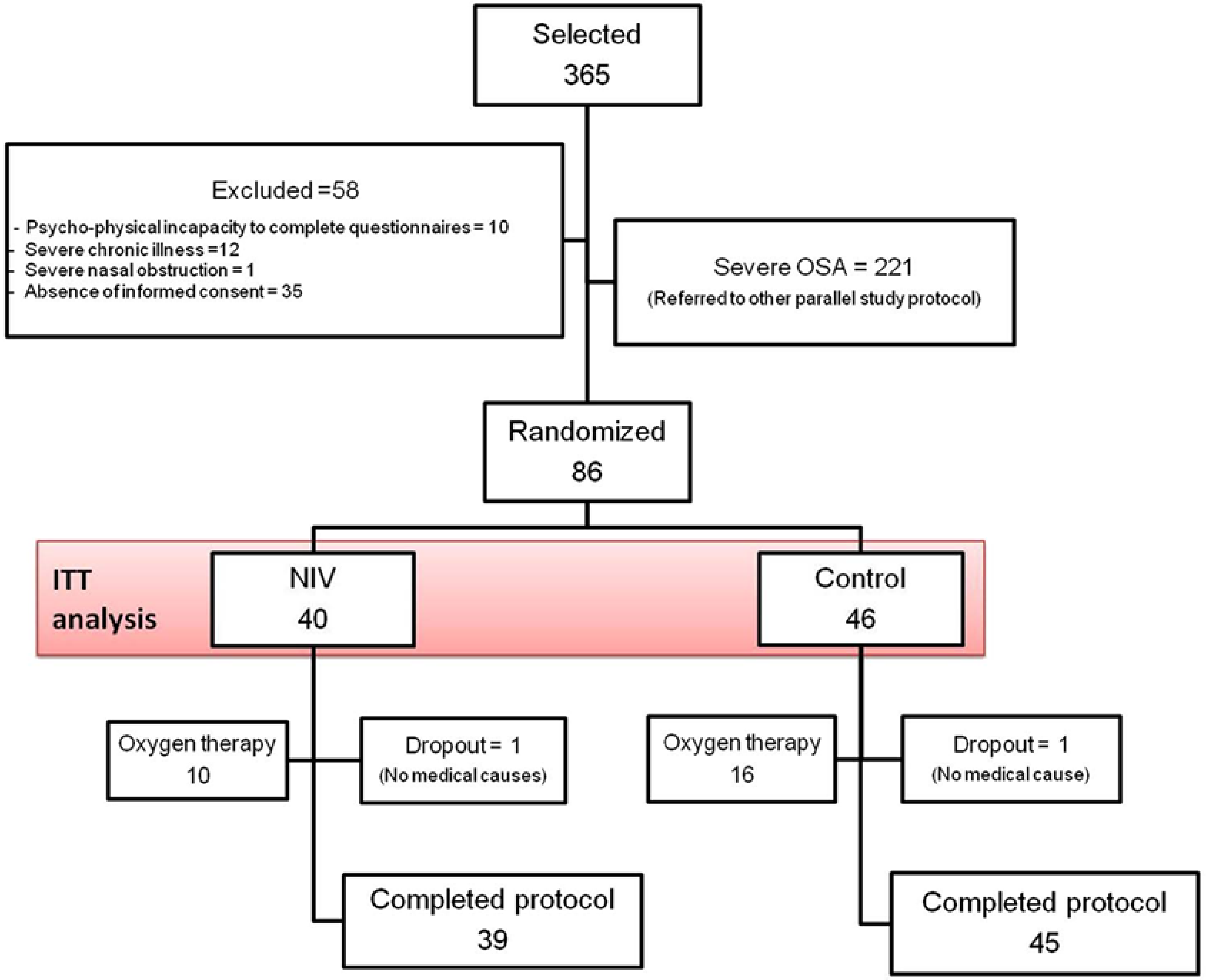
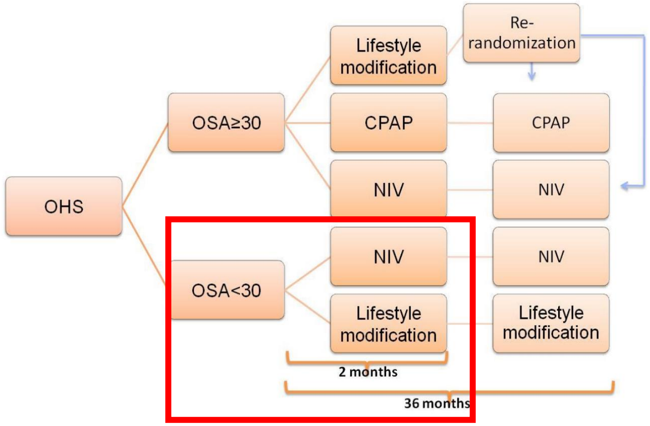


Figure 1 Flow chart of the study protocol. Of the 365 selected patients, 58 were excluded, 221 had severe OSA and 86 were randomised. A dropout in the control group was due to hospital admission requiring NIV treatment for more than 5 days. OSA, obstructive sleep apnoea; ITT, intention to treat; NIV, non-invasive ventilation.



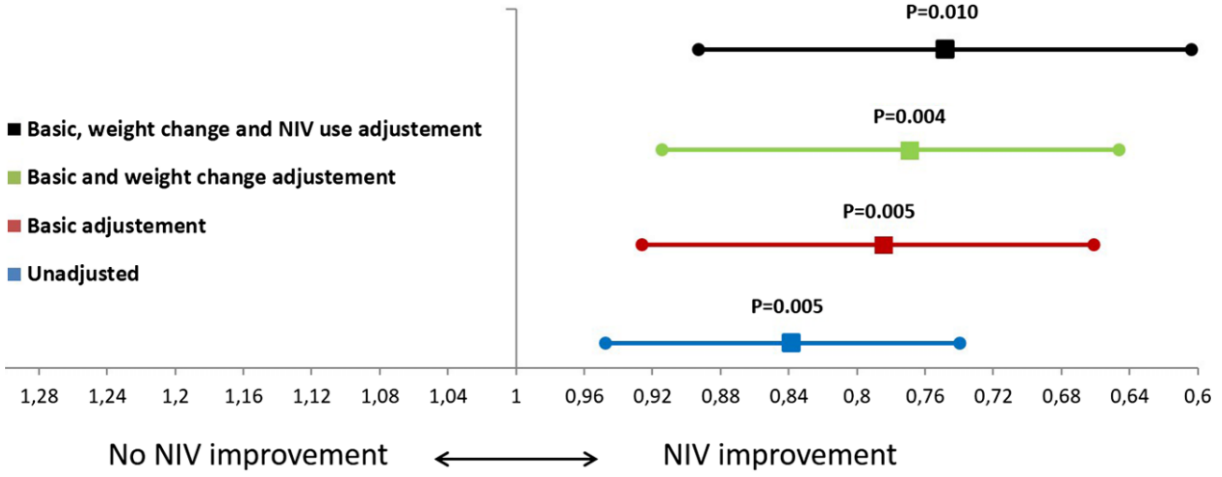
Masa JF, et al. Am J Respir Crit Care Med. 2015 Jul 1;192(1):86-95.

30↓, 2M, Primary outcome: $PaCO_2$

Table 2 Baseline measurements and changes with treatment related to the primary and secondary outcomes of pulmonary function and blood pressure measures

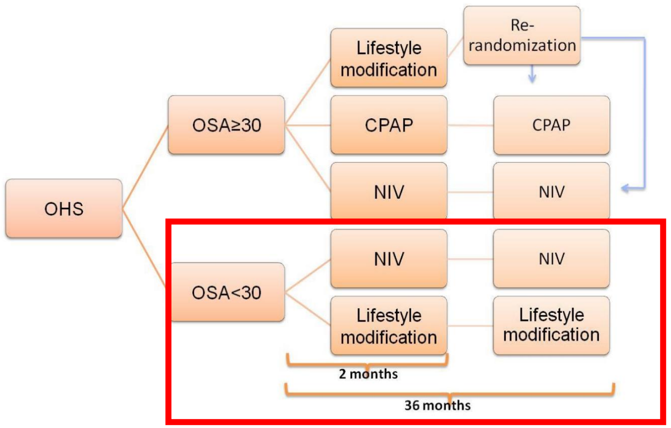
	Baseline, mean (SD)/median (IQR)		Intra-group differences, mean (95% CI)		p Value of inter-group differences§	
	NIV	Control	NIV	Control	Unadjusted	Adjusted
$PaCO_2$, mm Hg	*49 (4.0)*	*49 (3.5)*	**−6 (−7.7 to −4.2)‡**	**−2.8 (−4.3 to −1.3)‡**	0.006	0.019
Serum bicarbonate, mmol/L	*30 (4.1)*	*29 (3.8)*	**−3.4 (−4.5 to −2.3)‡**	**−1 (−1.7 to −0.2)***	0.000	0.004
pH	7.400 (0.040)	7.400 (0.030)	0.005 (−0.005 to 0.157)	0.031 (−0.008 to 0.147)	NS	–
PaO_2, mm Hg	64 (10)	67 (10)	**4.6 (0.5 to 8.8)***	1.4 (−2.6 to 5.5)	NS	–
FEV_1, %	72 (16)	80 (20)	1.8 (−2.7 to 6.4)	1.9 (−1.2 to 5.1)	NS	–
FVC, %	75 (21)	82 (20)	4.7 (−4.2 to 14)	2.9 (−0.5 to 6.3)	NS	–
6-MWD, m	309 (105)	349 (105)	29 (−16 to 74)	−7.2 (−25 to 11)	NS	–
Systolic BP, mm Hg	136 (18)	136 (15)	−4.2 (−11 to 2.5)	−4.3 (−10 to 1.7)	NS	–
Diastolic BP, mm Hg	*80 (16)*	*80 (18)*	0.5 (−5.3 to 6.2)	−1.2 (−5.4 to 2.9)	NS	–

Figure 2 Inter-group changes in arterial carbon dioxide tension ($PaCO_2$) (means and 95% of CIs) adjusted according to basic adjustments (baseline $PaCO_2$, age, sex, body mass index and apnoea–hypopnoea index), weight change and non-invasive ventilation (NIV) use (more or less than 4 hours/night).

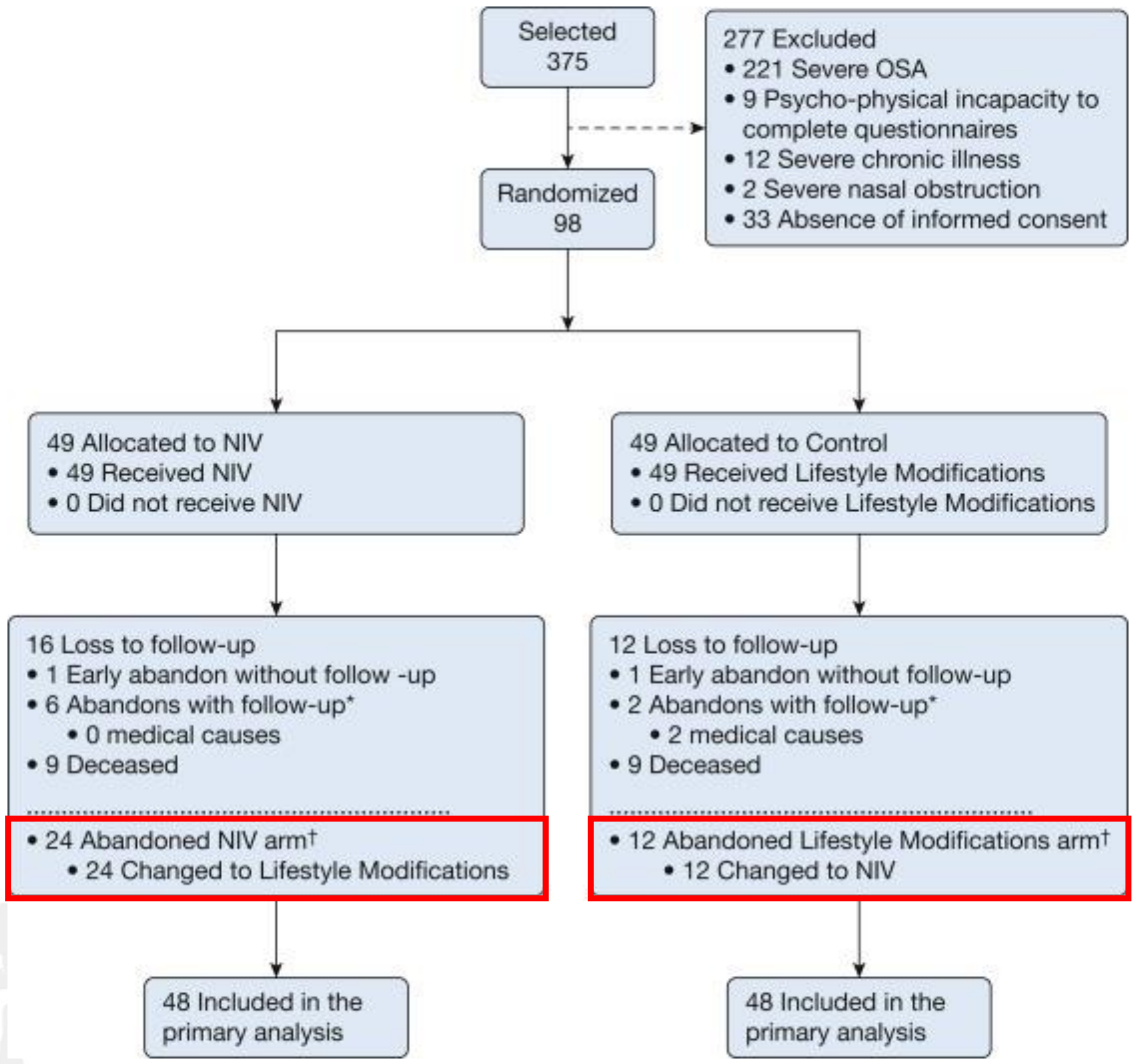


Masa JF, et al. Thorax. 2016 Oct;71(10):899-906.

30↓, 36M



- Median follow-up of 4.98 years
- NIV modality: volume targeted pressure support
- Lifestyle modification:1,000-calorie diet and the maintenance of correct sleep hygiene and habits.
- **Primary outcome: hospitalization days per year**
- Median adherence in the NIV arm: 3.68 h/d

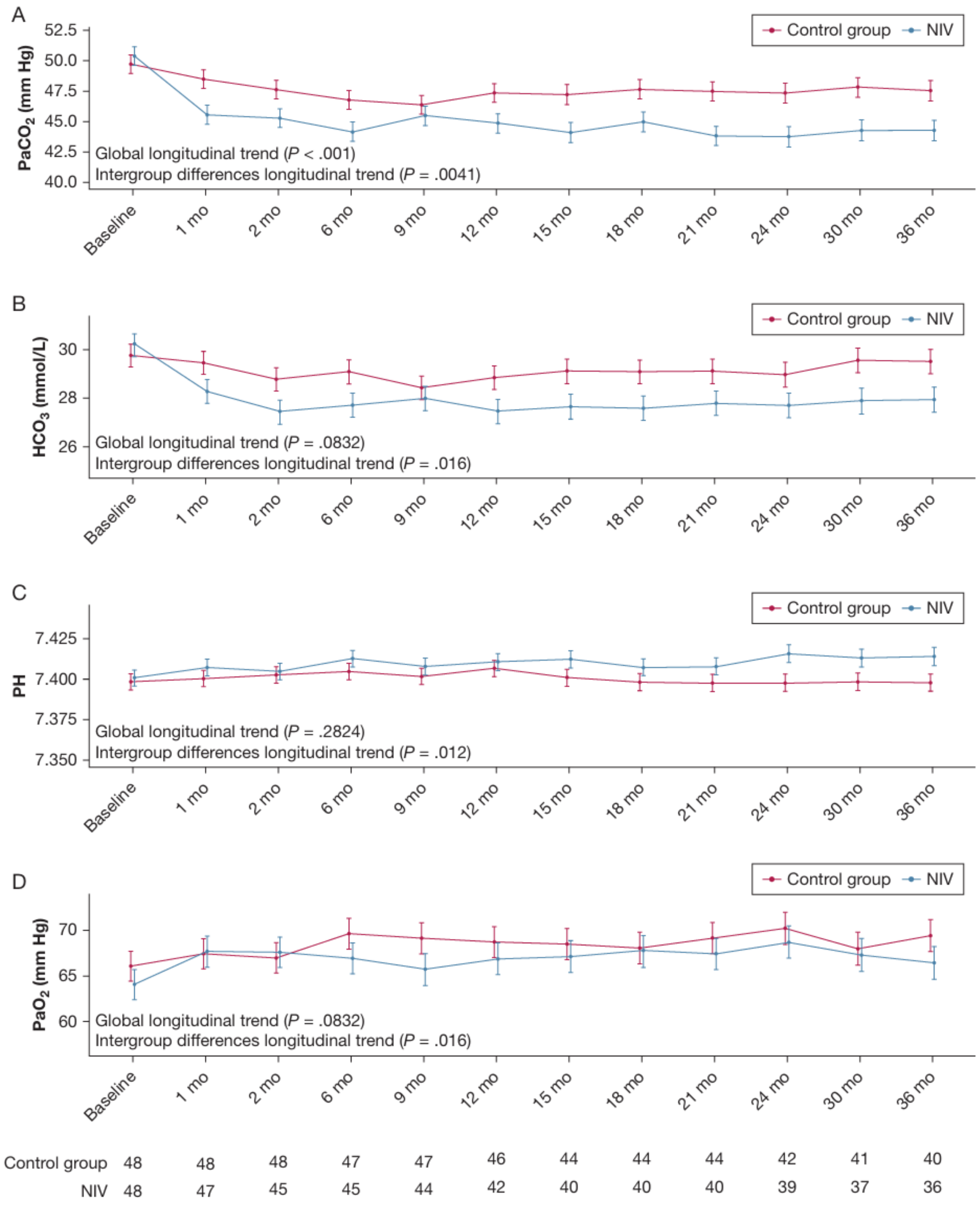


Masa JF, et al. Chest. 2020 Sep;158(3):1176-1186.

TABLE 2] Primary and Secondary Outcomes for the Control and NIV Groups

				Mixed-Effect Negative Binomial Regression Model		Mixed-Effect Cox Regression Model[a]	
Outcome	Control Group (n = 48)	NIV Group (n = 48)	Difference, Mean (95% CI)	Rate Ratio (95% CI)	P Value	Hazard Ratio (95% CI) With NIV	P Value
Primary outcome							
Days per year per patient							
ITT	2.60 ± 5.31	2.71 ± 4.52	0.11 (−1.89 to 2.11)	1.07 (0.44-2.59)	.882		
PP	2.32 ± 5.34	2.17 ± 4.30	−0.16 (−2.12 to 1.81)	0.92 (0.33-2.60)	.898		
Secondary outcomes							
Hospital admissions							
At least one							
ITT	29 (60)	26 (54)				0.99 (0.57-1.71)	.962
PP	23 (48)	19 (40)				0.83 (0.44-1.57)	.569
Events per year per patient							
ITT	0.37 ± 0.64	0.31 ± 0.47	−0.06 (−0.28 to 0.17)	0.93 (0.52-1.67)	.803		
PP	0.34 ± 0.66	0.28 ± 0.50	−0.05 (−0.29 to 0.18)	0.86 (0.43-1.73)	.667		
ED visits							
At least one							
ITT	36 (75)	32 (67)				0.73 (0.45-1.20)	.217
PP	30 (63)	22 (46)				0.45 (0.24-0.85)	.0112
Events per year per patient							
ITT	0.65 ± 0.74	0.54 ± 0.69	−0.11 (−0.4 to 0.18)	0.87 (0.55-1.37)	.547		
PP	0.66 ± 0.87	0.44 ± 0.71	−0.22 (−0.54 to 0.1)	0.69 (0.39-1.24)	.215		
Cardiovascular event							
ITT	11 (23)	10 (21)				0.96 (0.40-2.30)	.927
PP	7 (15)	8 (17)				1.21 (0.43-3.41)	.717
Mortality							
ITT	9 (19)	9 (19)				1.07 (0.41-2.82)	.893
PP	7 (15)	9 (19)				1.38 (0.50-3.79)	.529

time until the first ED visit



Nasal vs oronasal masks for home NIV in chronic hypercapnia: IPD meta-analysis

- 8 RCTs, 290 patients
- 4 for OHS, 3 for COPD, 1 for OHS and COPD
- Oronasal mask: 86%

Table 2 Baseline characteristics according to type of mask and diseases

Characteristics	Nasal (n=41)	Oronasal (n=249)	P values
Male, n (%)			
COPD	4 (21.1)	48 (53.3)	0.12
OHS	9 (40.9)	62 (39.7)	
Age (years)	62.1 (9.61)	61.5 (11.00)	0.95
COPD	64.0 (9.94)	63.9 (8.17)	
OHS	60.5 (9.24)	60.1 (12.10)	
BMI (kg·m^2)	35.4 (10.60)	38.3 (11.70)	0.13
COPD	26.3 (5.75)	26.2 (5.52)	
OHS	43.2 (6.90)	45.2 (8.17)	
FEV_1, L	1.54 (0.98)	1.56 (0.92)	0.80
COPD	0.74 (0.29)	0.68 (0.30)	
OHS	2.24 (0.81)	2.06 (0.77)	
FVC, L	2.59 (0.92)	2.49 (0.90)	0.74
COPD	2.33 (0.74)	2.39 (0.82)	
OHS	2.81 (1.02)	2.55 (0.95)	
$PaCO_2$, mm Hg	49.1 (4.12)	52.4 (5.89)	<0.001
COPD	49.7 (4.43)	54.8 (6.91)	
OHS	48.5 (3.85)	51.1 (4.75)	
PaO_2, mm Hg	65.2 (11.7)	60.6 (11)	0.008
COPD	61.2 (10.7)	55.1 (10.7)	
OHS	68.6 (11.6)	63.8 (10.0)	

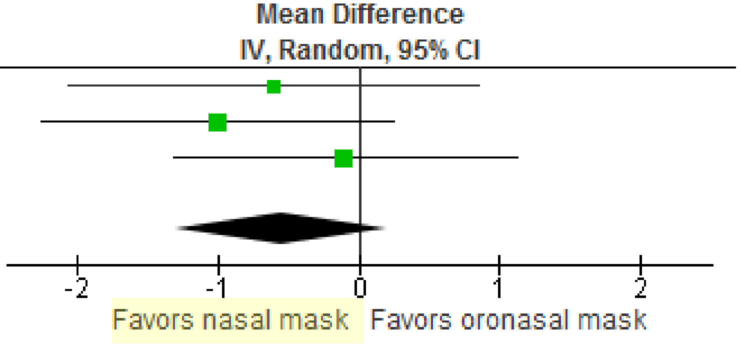
Masa JF, et al. Chest. 2020 Sep;158(3):1176-1186.

OSA
Nasal mask vs. Oronasal mask:
hrs/night

- RCTs

Study or Subgroup	Oronasal Mask Mean	SD	Total	Nasal Mask Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ebben 2014	4.6	2.2	14	5.2	1.7	14	26.3%	-0.60 [-2.06, 0.86]
Mortimore 1998	4.3	2.2	20	5.3	1.8	20	35.9%	-1.00 [-2.25, 0.25]
Rowland 2018	5.5	2.8	39	5.6	2.6	37	37.8%	-0.10 [-1.31, 1.11]
Total (95% CI)			**73**			**71**	**100.0%**	**-0.55 [-1.30, 0.19]**

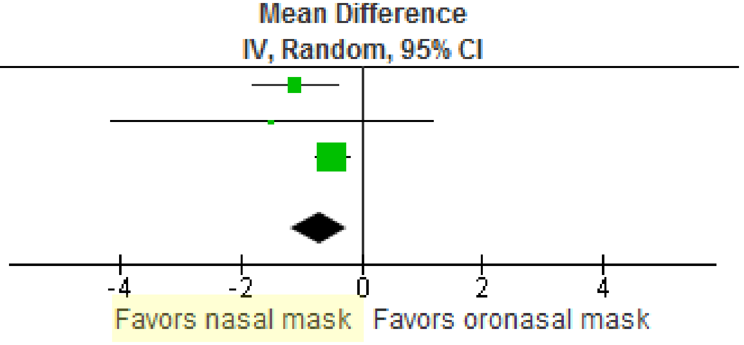
Heterogeneity: Tau² = 0.00; Chi² = 1.03, df = 2 (P = 0.60); I² = 0%
Test for overall effect: Z = 1.46 (P = 0.15)



- non-RCTs

Study or Subgroup	Oronasal Mask Mean	SD	Total	Nasal Mask Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bachour 2013	4.7	2.8	68	5.8	2.8	572	29.0%	-1.10 [-1.80, -0.40]
Beecroft 2003	4	2.3	3	5.5	1.8	41	2.9%	-1.50 [-4.16, 1.16]
Borel 2013	5	2.7	605	5.5	3.4	1443	68.1%	-0.50 [-0.78, -0.22]
Total (95% CI)			**676**			**2056**	**100.0%**	**-0.70 [-1.16, -0.24]**

Heterogeneity: Tau² = 0.06; Chi² = 2.87, df = 2 (P = 0.24); I² = 30%
Test for overall effect: Z = 3.00 (P = 0.003)

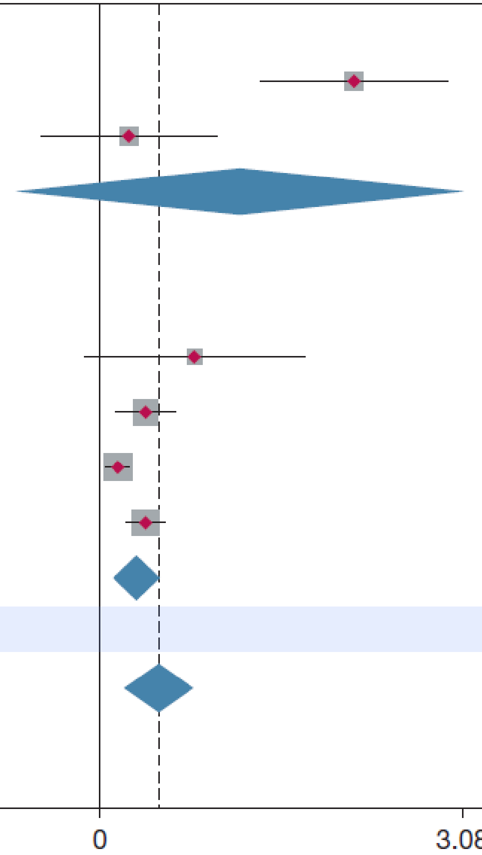


J Clin Sleep Med. 2019 Feb 15;15(2):301-334

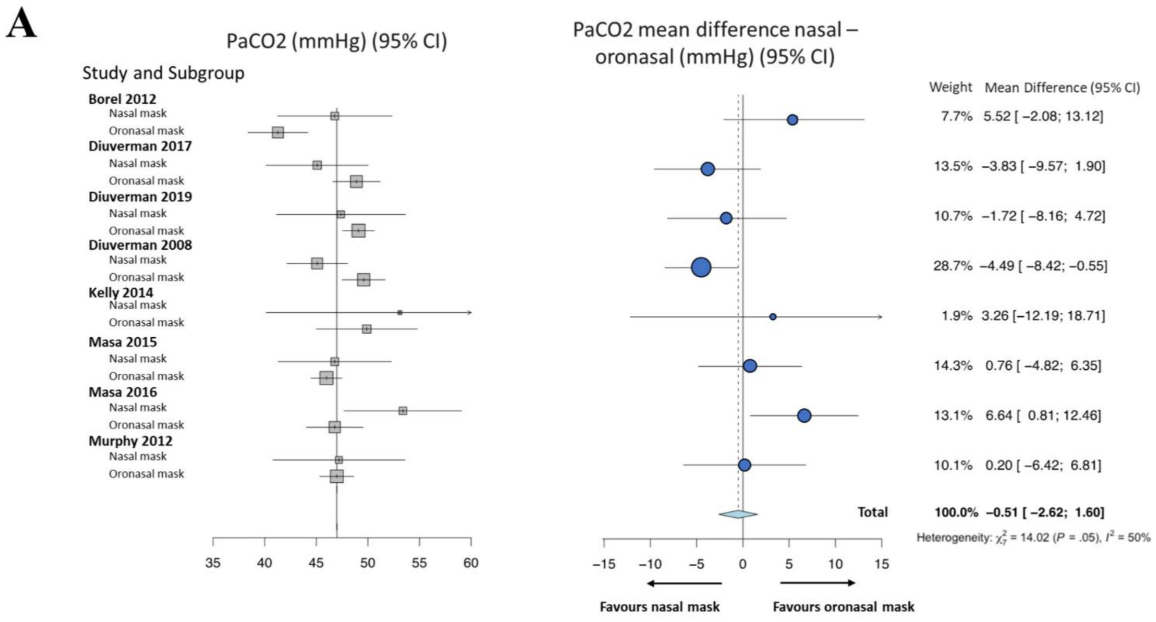
OSA
Nasal mask vs. Oronasal mask:
hrs/night

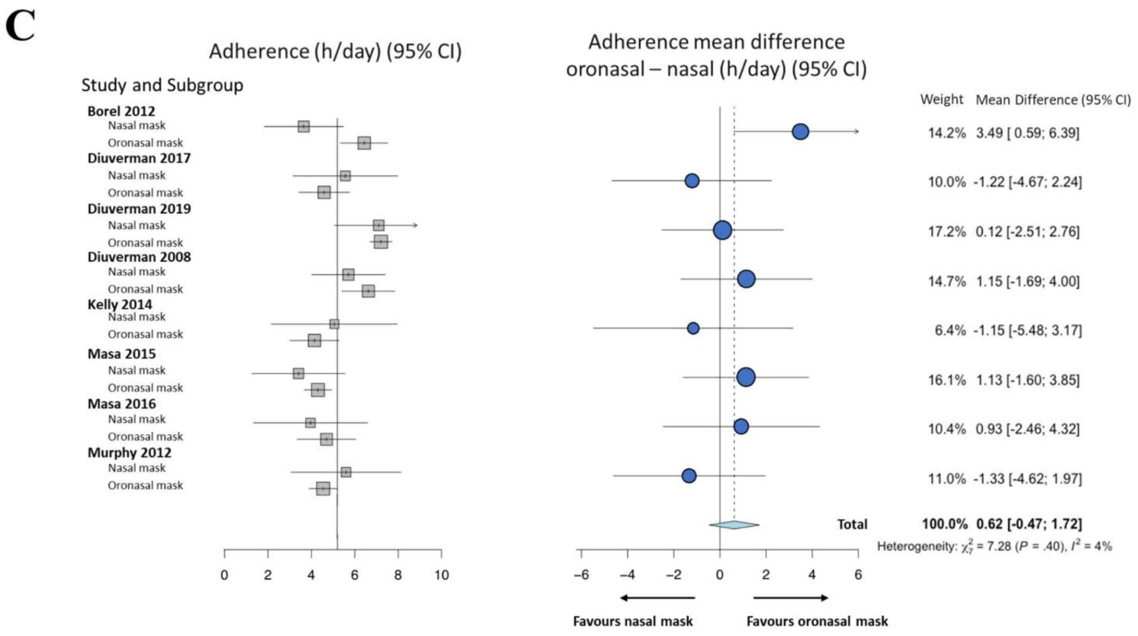
Study ID	SMD (95% CI)	% Weight
Randomized		
Mortimore, 1998	2.16 (1.37 to 2.96)	8.89
Ebben, 2014	0.25 (–0.50 to 0.99)	9.72
Subtotal (I^2 = 91.6%, *P* = .001)	1.20 (–0.68 to 3.08)	18.62
Nonrandomized		
Beecroft, 2003	0.80 (–0.13 to 1.73)	7.11
Bachour, 2013	0.39 (0.14 to 0.65)	22.52
Borel, 2013	0.16 (0.06 to 0.25)	26.55
Casanova, 2013	0.39 (0.23 to 0.55)	25.20
Subtotal (I^2 = 67.1%, *P* = .028)	0.31 (0.13 to 0.49)	81.38
Overall (I^2 = 84.1%, *P* = .000)	0.50 (0.21 to 0.79)	100.00

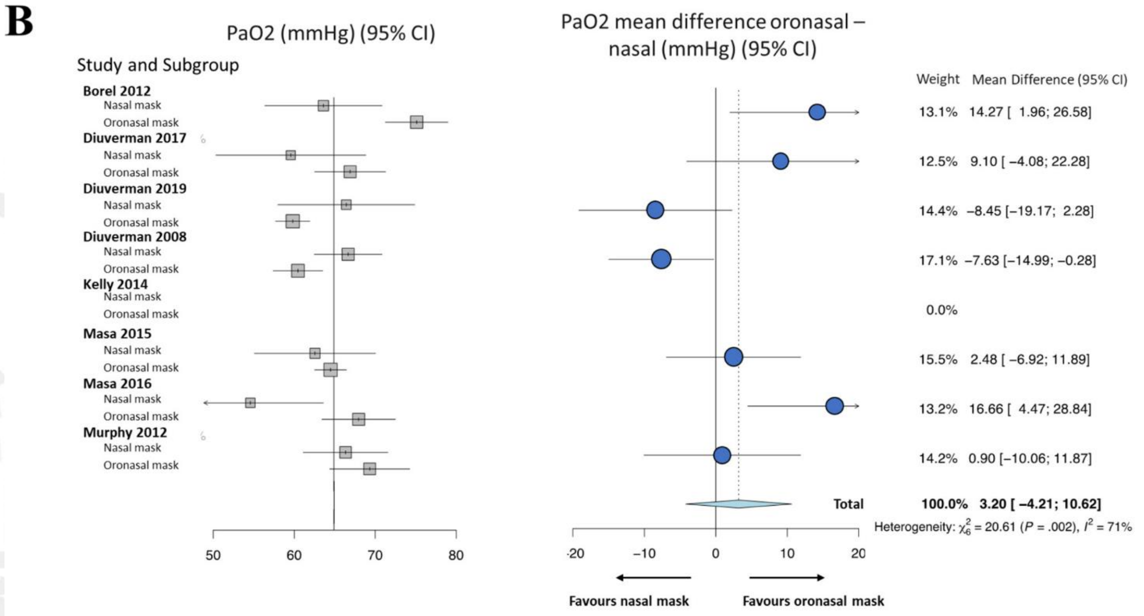
NOTE: Weights are from random effects analysis

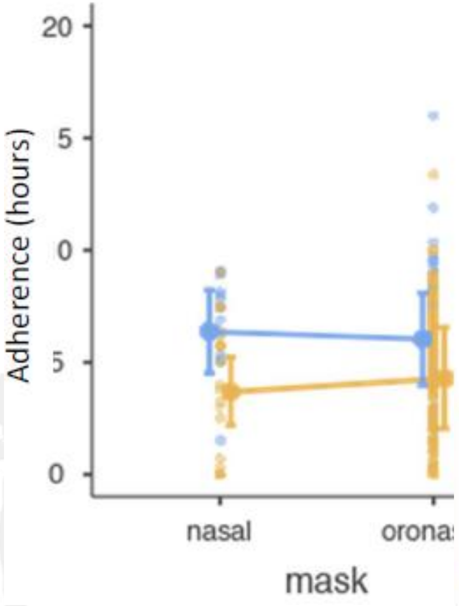


Andrade RGS, *et al.* Chest 2018;153:665-74.





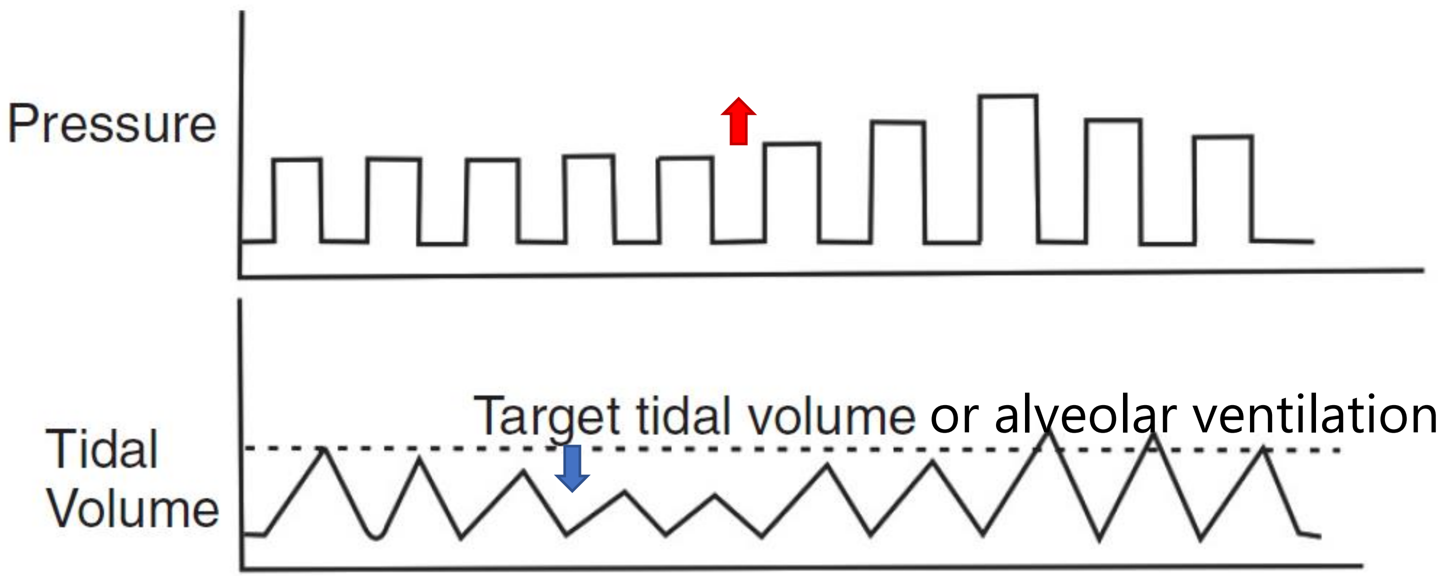




Thorax. 2021;76(11):1108-11

Volume-assured pressure support (VAPS)

- VAPS automatically adjusts the PS to deliver an adequate tidal volume/alveolar ventilation



Sleep medicine pearls, 3rd ed.

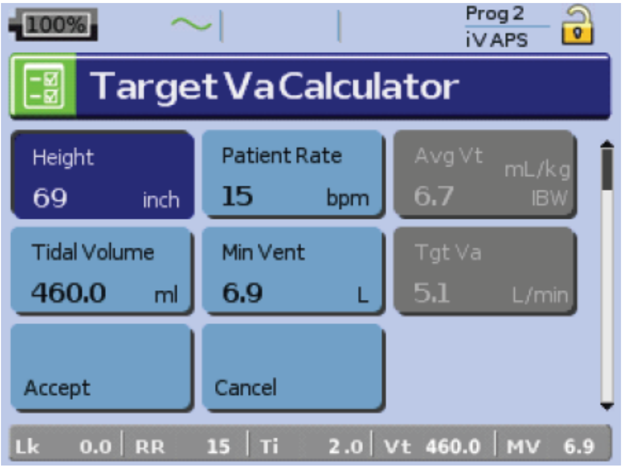
VAPS

Device	Intelligent VAPS (iVAPS)	Average VAPS (AVAPS)
Target	**Alveolar ventilation** = minute ventilation — dead space ventilation (based on height)	**Tidal volume**
EPAP	Set to maintain an open airway	Same
PS	Varies	Varies
Backup rate	iBR (intelligent backup rate) varies	Fixed
Settings	Target alveolar ventilation Height	Target tidal volume
	Max PS Min PS	Max IPAP min IPAP
	EPAP	EPAP
	Target backup rate	Backup rate
	Ti, Rise time, Trigger, Cycle	Ti, Rise time, Trigger, Cycle









Average Volume Assured Pressure Support and auto-EPAP (*AVAPS-AE*): Similar efficacy than ST mode in obesity hypoventilation

RCT in patients with OHS

Evaluating sleep quality with ST or AVAPS-AE

Primary outcome

- Improvement in objective sleep quality at 2 months following NIV setup in both groups
- No difference between the two groups

Secondary outcome

- Similar improvement in gas exchange between the two groups
- Similar adherence to NIV
- Similar improvement in health-related quality of life

Respirology

AVAPS-AE vs ST mode: A randomized controlled trial in patients with obesity hypoventilation syndrome

Patout et al. Respirology 2020; DOI: 10.1111/resp.13784

Summary

- OHS: BMI ≥ 30 kg/m^2 / daytime $PaCO_2$ ≥ 45 mmHg / sleep-disordered breathing
- Common: acute-on-chronic exacerbations, misdiagnosis

- For management of hospitalized patients in acute-on-chronic respiratory failure treated with NIV
  - patients be discharged on empiric NIV settings because of high risk of short-term (3 mo) mortality without therapy.
  - evaluation with a sleep study and PAP titration in the sleep laboratory as early as possible after discharge from the hospital, ideally within 3 months of discharge.

Thanks for your attention